DOCKET

SUPREME COURT
OF THE UNITED STATES

No. 09-1159
Title: Board of Trustees of the Leland Stanford Junior University, Petitioner
v.
Roche Molecular Systems, Inc., et al.
Docketed: March 25, 2010
Lower Ct.: United States Court of Appeals for the Federal Circuit
Case Nos.: (2008-1509, 2008-1510)
Decision Date: September 30, 2009
Questions Presented

---Date---	---Proceedings and Orders---
Mar 22 2010	Petition for a writ of certiorari filed. (Response due April 26, 2010)
Apr 21 2010	Order extending time to file response to petition to and including May 26, 2010.
Apr 23 2010	Brief amici curiae of Wisconsin Alumni Research Foundation, et al. filed.
Apr 26 2010	Brief amici curiae of Association of American Universities, et al. filed.
Apr 26 2010	Brief amicus curiae of Massachusetts Institute of Technology filed.
May 26 2010	Brief of respondents Roche Molecular Systems, Inc., et al. in opposition filed.
Jun 5 2010	Reply of petitioner Board of Trustees of the Leland Stanford Junior University filed. (Distributed)
Jun 8 2010	DISTRIBUTED for Conference of June 24, 2010.
Jun 28 2010	The Solicitor General is invited to file a brief in this case expressing the views of the United States.
Sep 28 2010	Brief amicus curiae of United States filed.
Oct 12 2010	Supplemental brief of respondents Roche Molecular Systems, Inc., et al. filed.
Oct 13 2010	DISTRIBUTED for Conference of October 29, 2010.
Nov 1 2010	Petition GRANTED.
Dec 3 2010	Consent to the filing of amicus curiae briefs, in support of either party or of neither party, received from counsel for the petitioner.
Dec 6 2010	Consent to the filing of amicus curiae briefs, in support of either party or of neither party, received from counsel for respondents.
Dec 16 2010	Joint appendix filed. (Statement of costs filed)
Dec 16 2010	Brief of petitioner Board of Trustees of the Leland Stanford Junior University filed.
Dec 16 2010	Supplemental joint appendix filed.
Dec 21 2010	The time to file respondent's brief on the merits is extended to and including January 25, 2011.
Dec 21 2010	Brief amicus curiae of Alexander M. Shukh, Ph.D. filed.
Dec 23 2010	SET FOR ARGUMENT Monday, February 28, 2011.
Dec 23 2010	Brief amicus curiae of the United States filed.
Dec 23 2010	Brief amicus curiae of American Intellectual Property Law Association filed.
Dec 23 2010	Brief amicus curiae of National Venture Capital Association filed.
Dec 23 2010	Brief amicus curiae of BayhDole25, Inc. filed.
Dec 23 2010	Brief amicus curiae of Birch Bayh filed.
Dec 23 2010	Brief amicus curiae of John Sutton filed.
Dec 23 2010	Brief amici curiae of Association of American Universities, et al. filed.
Jan 7 2011	CIRCULATED.
Jan 20 2011	Record received from U.S.C.A. for Federal Circuit. (1 box)
Jan 24 2011	Motion of the Acting Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument filed.
Jan 25 2011	Brief of respondents Roche Molecular Systems, Inc., et al. filed.
Feb 1 2011	Lodging request received from counsel for the respondents.

Feb 1 2011	Brief amici curiae of American Association of University Professors, et al. filed. (Distributed)
Feb 1 2011	Brief amici curiae of Intel Corporation, et al. filed. (Distributed)
Feb 1 2011	Brief amicus curiae of Pharmaceutical Research and Manufacturers of America filed. (Distributed)
Feb 1 2011	Brief amicus curiae of Biotechnology Industry Organization filed. (Distributed)
Feb 1 2011	Brief amicus curiae of Intellectual Property Owners Association filed. (Distributed)
Feb 14 2011	Reply of petitioner Board of Trustees of the Leland Stanford Junior University filed. (Distributed)
Feb 18 2011	Motion of the Acting Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument GRANTED.
Feb 28 2011	Argued. For petitioner: Donald B. Ayer, Washington, D. C., and Malcolm L. Stewart, Deputy Solicitor General, Department of Justice, Washington, D. C. (for United States, as amicus curiae.) For respondents: Mark C. Fleming, Boston, Mass.

PETITION FOR WRIT OF CERTIORARI

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Supreme Court, U.S.
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OFFICE OF THE CLERK

No. _____

In The
Supreme Court of the United States

BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY,
Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC.,
ROCHE DIAGNOSTICS CORPORATION,
ROCHE DIAGNOSTICS OPERATIONS, INC.,
Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Whether a federal contractor university's statutory right under the Bayh-Dole Act, 35 U.S.C. §§ 200-212, in inventions arising from federally funded research can be terminated unilaterally by an individual inventor through a separate agreement purporting to assign the inventor's rights to a third party.

PARTIES TO THE PROCEEDING

Pursuant to Rule 14.1(b), the following list identifies all of the parties appearing here and before the United States Court of Appeals for the Federal Circuit:

The petitioner here and plaintiff/counterclaim defendant-appellant below is the Board of Trustees of the Leland Stanford Junior University.

The respondents here and defendants/counterclaimants-cross-appellants below are Roche Molecular Systems, Inc., Roche Diagnostics Corporation, and Roche Diagnostics Operations, Inc.

RULE 29.6 STATEMENT

The Board of Trustees of the Leland Stanford Junior University has no parent corporation and does not issue stock.

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PETITION FOR A WRIT OF CERTIORARI

The Board of Trustees of the Leland Stanford Junior University ("Stanford") respectfully petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit in this case.

OPINIONS BELOW

The opinion of the United States Court of Appeals for the Federal Circuit (App. 1a-28a) is reported at *Board of Trustees of the Leland Stanford Junior University v. Roche Molecular Systems, Inc.*, 583 F.3d 832 (Fed. Cir. 2009). The Order of the U.S. Court of Appeals for Federal Circuit denying Stanford's Petition for Panel Rehearing and Rehearing En Banc is not reported. App. 75a-77a.

The opinion of the United States District Court for the Northern District of California is reported at 487 F. Supp. 2d 1099 (N.D. Cal. 2007). App. 29-74a.

STATEMENT OF JURISDICTION

The Federal Circuit entered judgment on September 30, 2009. App. 78a-79a. The Federal Circuit denied Stanford's Petition for Panel Rehearing and Rehearing En Banc on December 22, 2009. App. 75a-77a. This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS INVOLVED

"Each nonprofit organization or small business firm may, within a reasonable time after disclosure as required by paragraph (c)(1) of this section, elect to retain title to any subject invention." 35 U.S.C. § 202(a).

"[T]he contractor [must] disclose each subject invention to the Federal agency within a reasonable time after it becomes known to contractor personnel responsible for the administration of patent matters, and [] the Federal Government may receive title to any subject invention not disclosed to it within such time." 35 U.S.C. § 202(c)(1).

"If a contractor does not elect to retain title to a subject invention in cases subject to this section, the Federal agency may consider and after consultation with the contractor grant requests for retention of rights by the inventor subject to the provisions of this Act and regulations promulgated hereunder." 35 U.S.C. § 202(d).

"'The term 'subject invention' means any invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement." 35 U.S.C. § 201(e).

INTRODUCTION

The impact of the Federal Circuit's decision is without question: it immediately triggered a wave of discussion, commentary, and grave concern among the universities and other non-profits that have adhered to

the provisions of the Bayh-Dole Act, 35 U.S.C. §§ 200-212. At stake is the ownership of countless inventions made over the 30 years since the enactment of Bayh-Dole, as well as the expensive and onerous tasks that universities must now undertake in an attempt to manage the practical implications of the decision.

The Bayh-Dole Act establishes a comprehensive statutory scheme to allocate rights in "subject inventions" that arise from federally funded research. Prior to Bayh-Dole, the federal government generally held the rights to such inventions, which often went undeveloped. The Act establishes a framework under which "contractors," such as universities and other non-profit institutions that receive federal funding for research, retain the rights to subject inventions and must exercise those rights in ways that protect the government's and public's interests. The Act also limits the patent rights for individual inventors involved in the contractors' research, who may exercise rights in subject inventions only if the institution fails to exercise its statutory rights and, even then, only if the federal government consents following consultation with the institution.

Until the Federal Circuit's decision, universities believed they could retain ownership of inventions they sponsored through federal grants by following the procedures set forth in Bayh-Dole. The Federal Circuit's decision, however, allows for-profit companies to obtain shared ownership of these inventions simply by entering into a side-agreement with an inventor. Under the decision, a for-profit company does not need to follow any of the Bayh-Dole procedures to obtain this ownership, nor is it subject to any of the Bayh-

Dole restrictions, such as the use of royalties for further scientific research or education.

In arriving at its decision, the Federal Circuit ignored the clear mandate of the Bayh-Dole Act, choosing instead to rely on its own recent case law regarding the particular language that effects a "present assignment" of an invention. The Federal Circuit extended this case law to give a for-profit company a free and clear ownership interest in an invention made under the Bayh-Dole Act, even when it is aware of both the Bayh-Dole Act and the inventor's association with a research university. The Federal Circuit decision places the burden of monitoring for such activity, and dealing with the aftermath of violations, solely with the university. The impossible, impractical, and unfair one-sided burdens imposed on universities by the Federal Circuit's decision create an issue of enormous importance that should be addressed—and corrected—by this Court.

STATEMENT OF THE CASE

The Court of Appeals held that Stanford lacked standing to pursue its patent infringement claims against the Roche defendants based on the Roche defendants' assertion of ownership rights in the patents-in-suit. App. 27a-28a.

Patents-in-Suit and Ownership Issues

The patents-in-suit relate to methods for evaluating the effectiveness of anti-HIV therapies. App. 125a-126a; 127a-128a; 131a-132a. Stanford researchers, including Dr. Mark Holodniy, developed these methods in the early 1990s. App. 102a-105a. Dr. Holodniy is one

of three Stanford researchers named as inventors on the three patents-in-suit. App. 125a; 127a; 129a. Stanford is the named assignee of all three patents. App. 125a; 127a; 129a.

The National Institutes of Health provided funding for the Stanford research project out of which the patents arose. App. 109a, ¶ 8; 114a-115a, ¶ 3. This clinical research was performed under at least two federal grants: one providing funding for AIDS-related clinical trials and another establishing Stanford as a Center for AIDS Research. *Id.*

Dr. Holodniy joined Stanford as a Research Fellow in the Department of Infectious Disease in 1988. App. 94a. Dr. Holodniy signed Stanford's standard Copyright and Patent Agreement (the "Stanford Agreement") when he began his work at Stanford in mid-1988. *See* App. 118a-121a. In the Stanford Agreement, Dr. Holodniy "agree[d] to assign" his inventions to Stanford. App. 119a, ¶ 2. Additionally, the Stanford Agreement prohibited Dr. Holodniy from creating "patent obligations in conflict with this agreement." App. 120a.

In 1989, Dr. Holodniy entered into a "Visitor's Confidentiality Agreement" ("VCA") with Cetus, a local biotechnology company. App. 122a-124a. Under the VCA, Dr. Holodniy agreed that he "will assign and do[es] hereby assign" his rights to Cetus to inventions conceived and/or reduced to practice as a consequence of his access to Cetus's information and facilities. App. 123a, ¶ 3. Cetus later transferred its interest in the VCA to Roche. *See* App. 5a.

After Dr. Holodniy ceased visiting Cetus, the Stanford inventors conceived and reduced to practice the clinical inventions of the patents-in-suit. *See* App. 102a-105a.

Stanford's inventions were "subject inventions" under the Bayh-Dole Act of 1980, because they were conceived or reduced to practice using federal funding. The Act generally provides that a university (as a nonprofit organization) may elect to retain title to any inventions that arise out of federally funded research projects.

On April 6, 1995, Stanford gave formal notice to the federal government that it intended to elect to retain title to the patents-in-suit under the Bayh-Dole Act, 35 U.S.C. §§ 200-212. *See* App. 115a-116a.

Decisions Below

The district court upheld Stanford's standing to bring patent infringement claims against Roche, based on (1) the agreement between Dr. Holodniy and Stanford, under which he agreed to assign his invention rights to Stanford and agreed not to enter into inconsistent agreements, (2) the Bayh-Dole Act, which gave Stanford ownership of the patents because they resulted from federally funded research, and (3) Stanford's recordation of its title at the U.S. Patent Office and the National Institutes of Health. App. 59a-62a.

The Federal Circuit reversed the district court's judgment as to the standing issue. App. 78a. The Court held that because of the VCA between Dr. Holodniy and Cetus, Roche had an ownership interest in the

patents that defeated Stanford's standing to sue Roche for infringement. App. 27a-28a.

The Court rejected Stanford's statutory argument based on the Bayh-Dole Act. App. 18a-21a. As provided by the Bayh-Dole Act, a university may "elect to retain title to any subject invention." 35 U.S.C. § 202(a), reproduced at App. 84a. If the university "does not elect to retain title to a subject invention in cases subject to this section, the Federal agency may consider and after consultation with the contractor grant requests for retention of rights by the inventor." 35 U.S.C. § 202(d). Relying on these provisions, Stanford argued that the Bayh-Dole Act limited Dr. Holodniy to a contingent right that would vest only if Stanford did not elect to retain title within a reasonable period of time. App. 18a-19a. As a result, even assuming that Dr. Holodniy transferred his contingent right to Cetus, that right was extinguished upon Stanford's election to retain title.

Roche never argued, and the Court did not find, that Stanford's statutory election to retain title was deficient in any way under the Act. Instead, the Court of Appeals' decision turned solely on a formalistic distinction between present and future assignments. The Court concluded that the language in the Stanford Agreement in which Dr. Holodniy "agree[d] to assign" his invention rights to Stanford constituted only a promise to assign those rights in the future. App. 13a. The Court further concluded that the later-in-time VCA included present "do[es] hereby assign" language that conveyed an ownership interest to Cetus immediately upon conception of the inventions. App. 14a.

Based on those conclusions and despite the Bayh-Dole Act, the Court awarded Roche title to Dr. Holodniy's ownership interests, holding that the "present" assignment language in the VCA trumped the "future" assignment language in the Stanford Agreement. App. 13a-14a.

REASONS FOR GRANTING THE PETITION

I. The Bayh-Dole Act Provides a Framework for the Ownership of Inventions Made with Government Funding.

Before the Bayh-Dole Act, ownership of federally funded inventions originally vested in the federal government. A patchwork of federal agencies made decisions about subsequent assignments and other ownership issues. Through the Bayh-Dole Act, Congress intended to end this uncertainty regarding title to federally funded inventions and thereby spur commercialization of federally funded inventions to the benefit of the American public.

Congress enacted the Bayh-Dole Act ("the Act"), *inter alia*, "to promote the utilization of inventions arising from federally sponsored research or development," "to promote the commercialization and public availability of inventions made in the United States by United States industry and labor," and "to promote collaboration between commercial concerns and nonprofit organizations, including universities." 35 U.S.C. § 200. Congress attempted to accomplish these goals by vesting ownership of "subject inventions" in "small business firms" and "nonprofit organizations," including universities such as Stanford, rather than the federal government. 35 U.S.C. §§ 200-212. "Subject

inventions" are defined to be inventions conceived or first reduced to practice in the performance of work under a federal funding agreement.

Under the Act, nonprofit organizations like Stanford have the right to "elect to retain title to any subject invention" except in limited circumstances not at issue in this case in which the federal government or individual inventors may retain title. 35 U.S.C. § 202(a).

The provisions of the Act do not allow unrestricted assignment of subject inventions by nonprofit organizations or individual inventors to commercial entities. Instead, the Act places careful restrictions on assignments, licenses, and use of royalties related to any subject inventions. For example, section 202(c)(7)(A) specifically requires all funding agreements to contain "***a prohibition*** upon the assignment of rights to a subject invention in the United States without the approval of the federal agency." 35 U.S.C. § 202(c)(7)(A) (emphasis added). Similarly, section 204 restricts a nonprofit organization from "grant[ing] to any person the exclusive right to use or sell any subject invention in the United States unless such person agrees that any products embodying the subject invention or produced through the use of the subject invention will be manufactured in the United States" unless a waiver is obtained. 35 U.S.C. § 204. As to royalties, the Bayh-Dole Act requires that the "balance of any royalties or income earned by the contractor with respect to subject inventions, after payment of expenses (including payments to inventors) incidental to the administration of subject inventions, be utilized for the

support of scientific research or development." 35 U.S.C. § 202(c)(7)(C).

Congress sought to achieve these ends by setting up an ownership structure in which title to federally funded inventions vests with the university so long as it makes an ownership election within a reasonable period of time after the invention is made. In return, those institutions agree to use their best efforts to commercialize those inventions for public benefit. By creating certainty as to the title of federally funded inventions, the Act encouraged collaboration between private companies and universities and other non-profit research institutions in a manner that would benefit the public.

Under the Federal Circuit's decision, private, for-profit companies can obtain the benefits of federal research funding to create inventions, while avoiding the obligation to use royalties to benefit education and research and sidestepping the other conditions of federal funding under the Act. The Federal Circuit's decision will also permit for-profit commercial entities to acquire invention rights for the purpose of "shelving" the technology to deprive their competitors of the use of the technology, contrary to the intent of the Bayh-Dole Act to foster commercialization of federally funded inventions.

The federal government has spent billions of dollars on federally funded research projects subject to the Bayh-Dole Act. Universities and other research institutions, through the commercialization of federally funded inventions intended by the Bayh-Dole Act, fund their further research and development

efforts through patent royalties, as contemplated by the Act.

II. Under the Federal Circuit's Decision, an Individual Inventor Can Defeat a Research Institution's Right to Elect to Retain Title to a Federally Funded Invention, the Federal Government's Rights Under the Bayh-Dole Act, and the Rights of Co-Inventors.

The Federal Circuit's decision radically upends the Bayh-Dole Act, a carefully balanced federal law intended to foster commercialization of federally funded inventions to the benefit of the American public. Under the decision, an individual inventor may prospectively assign to a for-profit, commercial entity the invention rights to a federally funded invention yet to be conceived, thereby circumventing the statutory rights of the nonprofit organization that received the federal funding. This result contravenes the plain language and structure of the Bayh-Dole Act, which contemplates that a nonprofit organization (such as a research institution or university) that receives federal research funds will have the right to elect ownership to resulting inventions except in cases where it fails to disclose the invention, or fails to file a timely patent application. If the nonprofit does not satisfy these requirements, then the federal government may receive title. 35 U.S.C. § 202(c)(1). The Bayh-Dole Act makes no provision for third-party commercial entities to take title if the nonprofit fails to take steps to retain or secure title.

The Federal Circuit's conclusion that Dr. Holodniy effectively assigned his rights to the patents-in-suit to Cetus necessarily and erroneously takes as its starting

point that Dr. Holodniy had a right to make an assignment that could extinguish Stanford's interests in the inventions. Under the Bayh-Dole Act, however, Stanford had a statutory right to make an ownership election within a reasonable period of time that could not be overridden by the inventor's agreement. The university's statutory right to title arises from the language and structure of the Bayh-Dole Act. Section 202(a) of the Bayh-Dole Act provides: "Each nonprofit organization . . . may, within a reasonable time after disclosure as required by paragraph (c)(1) of this section . . . elect to retain title to any subject invention." 35 U.S.C. § 202(a). An inventor may not defeat the research institution's Section 202(a) right to elect retain title through a side agreement with a for-profit third party.

Further, the Act defines inventions that are subject to its provisions broadly. A subject invention under the Bayh-Dole Act is defined as one that is "*conceived or first actually reduced to practice* in the performance of work under a [federal] funding agreement." 35 U.S.C. § 201(e) (emphasis added). The Act thus expressly encompasses inventions that were either conceived or reduced to practice using government funding. This is significant because it contemplates that some inventions may have been conceived earlier without using government funding, but they are still subject to the Act if they were later reduced to practice for the first time using government funding. The Act does not exclude inventions from its coverage merely because some inventive work was accomplished without government funding. Here, Stanford presented substantial evidence showing that the patents in suit were *both* conceived and reduced to practice under federal grants.

The Act carefully restricts the circumstances in which an individual inventor may acquire an ownership interest in a federally funded invention. The inventor's ownership rights vest only if the research institution chooses not to exercise its statutory right to retain title *and* the federal government consents after consultation with the research institution. *See* 35 U.S.C. § 202(d). Section 202(c)(7)(A) also requires all funding agreements to contain "a prohibition upon the assignment of rights to a subject invention in the United States without the approval of the Federal agency." 35 U.S.C. § 202(c)(7)(A). The Stanford Agreement signed by Dr. Holodniy, before the execution of the VCA, contained just such a provision. App. 120a, ¶ 6.

Against this clear statutory backdrop, the Federal Circuit held that Dr. Holodniy's side agreement with Cetus gave Roche ownership rights in the patents-in-suit that defeated Stanford's infringement claims. Although Stanford had a prior agreement with Dr. Holodniy under which he "agreed to assign" his invention rights to Stanford, the Court held that this agreement did not effect a present assignment, but rather constituted a promise to assign those rights in the future. App. 13a. The Court concluded that Dr. Holodniy had, and effectively transferred to Cetus, patent ownership rights in the federally funded inventions. App. 14a. The Court deemed Stanford's later election to retain title under the Bayh-Dole Act to be subject to Dr. Holodniy's earlier private assignment agreement with Cetus. App. 19a-20a.

The Federal Circuit provided no reason why its present assignment case law should properly be extended to provide *clear* title even when it is subject

to an *earlier* promise to assign. There is no reason it should be applied such a manner. As a result of his earlier agreement with Stanford, the most that Dr. Holodniy could later assign—whether using the "present assignment" language or not—was an interest that was subject to his contract with Stanford. As that contract retained ownership for government funded inventions, Dr. Holodniy could not convey any ownership interest in the inventions of the patents-in-suit. *See* App. 119a.

Nor did the Federal Circuit's decision explain why a present assignment could trump the Bayh Dole Act's restrictions on how an inventor could claim title. Here, as explained above, the Bayh-Dole Act allowed Dr. Holodniy to obtain title only if Stanford declined to retain title. Nonetheless, the Federal Circuit's decision held that the present assignment to Cetus can wholly evade this statutory framework and give to Cetus title through Dr. Holodniy even though Dr. Holodniy was precluded from obtaining that title for himself. App. 13a-14a; 19a-20a.

Additionally, when patents have multiple inventors, the Federal Circuit's decision permits a single inventor to undermine the intellectual property rights of his or her co-inventors. It is very common that patents filed by research institutions result from the collaboration of multiple contributors, who may be named as co-inventors. This was the case with Dr. Holodniy. He was one of the three named inventors on the patents in question. App. 125a; 127a; 129a; 131a. Under the Federal Circuit's decision, a single inventor could alienate his rights for a fee, usurping the rights of co-inventors to share in any financial benefits from commercializing the intellectual property. The effect of

the Federal Circuit's decision is exacerbated when the contributing co-inventors are employed by separate research institutions. These inequities are expressly avoided by the Bayh-Dole Act, but are inevitable consequences of the Federal Circuit's decision.

If the Federal Circuit's decision is allowed to stand, the rights of contracting institutions, like Stanford, can be unilaterally terminated by the inventor. Further, applying the same reasoning, the federal government's rights under the statute in the invention would also be terminated unilaterally by the inventor if she or he assigns the rights to a third party. To the contrary, the Bayh-Dole Act plainly contemplates that inventors like Dr. Holodniy have rights only if the government consents (after consultation with the contractor). Thus, the Federal Circuit's holding means that the federal government has no rights unless the inventor consents. The Federal Circuit's decision stands the Bayh-Dole Act on its head. All of the statutory protections to the government and public under the statutory scheme, including the government's nonexclusive license, the made-in-America restrictions, the requirement to exploit the invention, and the requirement to invest royalties back into research would be eliminated.

III. The Federal Circuit's Decision Will Cloud Title to Federally Funded Inventions and Impose Massive Costs on Research Institutions.

The Federal Circuit's decision also eviscerates the certainty regarding title to federally funded inventions intended by Congress. It may no longer be safe for universities (or their commercial counterparts and

partners) to assume that the research institution will have the right to elect to retain title to federally funded inventions. Any individual inventor's side agreement could cloud the title for subject inventions made over the last 30 years.

Under the Federal Circuit's decision, before a research institution engages in the very technology transfer activities intended by the Act, it may be required to embark on wide-ranging investigations to ensure that no individual inventor on the project has purposefully or inadvertently entered into a side agreement that gives rights in the invention to a third party.

The need for this burdensome investigation is exacerbated by the Federal Circuit's holding that Stanford would be presumed to know of Dr. Holodniy's side agreement with Cetus under the legal fiction of "constructive or inquiry notice." App. 16a. There is no dispute that Stanford did not have actual knowledge of the agreement.

Requiring a research institution or university to police every agreement into which its researchers may enter would consume substantial resources and yet provide no assurances. Even with substantial investigation, a university may be unable to ascertain what rights have been transferred to third parties because university researchers have been entering into "side agreements" for decades, often without appreciating the import of those agreements. Individual researchers may well not have retained their side agreements or even remember that they have entered into such agreements.

The Federal Circuit's decision does not mention, much less consider, whether it was appropriate to require the university, rather than the for-profit company, to carry or share this enormous burden. Under the facts in the case, Cetus knew of Dr. Holodniy's association with Stanford when it entered into the consulting agreement. App. 122a-124a. Cetus was also aware of the Bayh-Dole Act. App. 136a-137a. Despite Cetus's actual knowledge, the Federal Circuit nonetheless chose to shift the burden to Stanford based on a "constructive knowledge" conclusion. Contrary to the Federal Circuit's decision, it would be far more efficient, and would better serve the public interest, to impose some or all of this burden on the for-profit company, particularly when it has actual knowledge that Bayh-Dole may be implicated.

The monumental one-sided burdens imposed by the Federal Circuit's decision significantly undermine the central goals of the Bayh-Dole Act, including commercialization of federally funded inventions for the benefit of the public.

IV. Universities Cannot "Contract Around" the Federal Circuit's Decision.

In response to the Federal Circuit's decision, universities may choose to revise their contracts with researchers and inventors to excise the use of the phrase "agrees to assign" language and instead use the word "assigns" or the phrase "hereby does assign."

In practice, however, this is no solution. For decades, universities like Stanford – including the University of California, Massachusetts Institute of Technology, the University of Wisconsin, and Yale

University—have included "agree to assign" language like that in the Stanford Agreement in their own contracts and policies. Indeed, in the nearly 30 years since Bayh-Dole's passage, universities have entered into innumerable agreements with individual inventors using "agree to assign" language. Under the Federal Circuit's decision, the title to decades of federally funded inventions may be thrown into doubt for decades to come.

Further, such an approach is, at best, only a partial solution and remains fraught with uncertainty. Using "present" assignment language may be ineffective under the Federal Circuit's decision if the contractor has executed a contract like Dr. Holodniy's VCA before signing the University's contract. In such situations, far-reaching language in such a side agreement could be used by for-profit companies to argue they have rights to inventions that are subsequently made with federal funding. Moreover, title could also be unclear if the university and a third party held competing present assignments at the time of invention. This cloud on universities' ownership of patent or other intellectual property rights will make it more difficult to license and commercialize intellectual property. Consequently, the intellectual property will be less widely disseminated and used. This uncertainty caused by the Federal Circuit's decision undermines the Bayh-Dole Act.

V. This Important Statutory Issue Should Be Addressed Now.

There is an extraordinary public interest in a clear and immediate resolution of the question presented by Stanford's petition. Although the Federal Circuit's

decision addresses an issue of first impression, this is not a matter that should be permitted to "percolate" over time through the lower courts. The important federal interests promoted by the Bayh-Dole Act—including billions of dollars invested by the government annually into research—are presently and substantially compromised by the Federal Circuit's decision. Likewise, universities and other research institutions face immediate and substantial administrative and financial burdens if the Federal Circuit's decision is not addressed by this Court. Indeed, several universities joined with Stanford in asking the Federal Circuit to address the issue en banc. The Federal Circuit's decision has triggered a flurry of commentary and concern, including commentary from one of the authors of the Bayh-Dole statute, Senator Bayh.[1]

This Court should not wait for a circuit split before addressing this issue. Although the Federal Circuit does not have exclusive jurisdiction of ownership disputes under the Bayh-Dole Act, such disputes are most likely to arise in patent infringement cases, which are subject to the exclusive jurisdiction of the Federal Circuit under 28 U.S.C. § 1295. The Federal Circuit declined to rehear the case en banc and thus a different conclusion is not likely to be forthcoming from the Federal Circuit. Other Circuits have decided only a very small handful of cases even tangentially

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[1] Birch Bayh, Joseph P. Allen, & Howard W. Bremer, *Universities, Inventors and Bayh-Dole*, 79 Pat., Trademark & Copyright J. (PTCJ) 167 (2009).

involving the Bayh-Dole Act,[2] and there is no way to predict how, when, and whether another Circuit may reach the statutory ownership issues raised squarely in this case.

The Federal Circuit's decision implicates substantial federal interests for the additional reason that the Federal Circuit's reasoning would also permit an individual inventor to terminate the *government's* rights with regard to the federally funded invention. Moreover, permitting unilateral assignment by an individual inventor to circumvent the statutory scheme deprives the government and the public of the benefits intended under the Act, including requirements that the invention be made in the United States and that royalties be invested back into research.

Immediate review is necessary to resolve this important federal question.

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[2] *See, e.g., Univ. of Pittsburgh v. Townsend*, 542 F.3d 513 (6th Cir. 2008); *Fenn v. Yale Univ.*, 184 F. App'x 21, 2006 WL 1408336 (2d Cir. 2006).

CONCLUSION

For these reasons, the petition for a writ of certiorari should be granted.

Respectfully submitted,

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March 22, 2010

APPENDIX

APPENDIX

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APPENDIX A

United States Court of Appeals for the Federal Circuit

2008-1509, -1510

[Decided September 30, 2009]

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiff/Counterclaim Defendant-Appellant,

and

THOMAS MERIGAN and MARK HOLODNIY,

Counterclaim Defendants,

v.

ROCHE MOLECULAR SYSTEMS, INC., ROCHE DIAGNOSTICS CORPORATION, ROCHE DIAGNOSTICS OPERATIONS, INC.,

Defendants/Counterclaimants-Cross Appellants.

Ricardo Rodriguez, Cooley Godward Kronish LLP, of Palo Alto, California, argued for plaintiff/

counterclaim defendant-appellant. With him on the brief were Michelle S. Rhyu, Lori Ploeger and Benjamin G. Damstedt.

Adrian R. Pruetz, Pruetz Law Group LLP, of El Segundo, California, argued for defendants/counterclaimants-cross appellants. With her on the brief were Erica J. Pruetz and Lauren M. Gibbs. Of counsel on the brief were Brian C. Cannon and Charlie Y. Chou, Quinn Emanuel Urquhart Oliver & Hedges, LLP, of Redwood Shores, California. Of counsel was Pablo D. Arredondo, of New York, New York.

Appeals from the United States District Court for the Northern District of California in case no. 05-CV-04158, Judge Marilyn H. Patel.

DECIDED: September 30, 2009

Before LINN, PROST, and MOORE, Circuit Judges.

LINN, Circuit Judge.

The Board of Trustees of the Leland Stanford Junior University ("Stanford") appeals a final judgment that the asserted claims of U.S. Patents No. 5,968,730 ("'730 patent"), No. 6,503,705 ("'705 patent"), and No. 7,129,041 ("'041 patent") are invalid for obviousness. Bd. of Trs. v. Roche Molecular Sys., Inc., 563 F. Supp. 2d 1016 (N.D. Cal. 2008) ("Invalidity Opinion"). Roche Molecular Systems, Inc., Roche Diagnostics Corporation, and Roche Diagnostics Operations, Inc. (collectively, "Roche") cross-appeal that part of the district court's judgment relating to

Roche's ownership, license, and shop rights to the patents-in-suit. Bd. of Trs. v. Roche Molecular Sys., Inc., 487 F. Supp. 2d 1099 (N.D. Cal. 2007) ("Contract Opinion").

Because the district court correctly found that Roche's counterclaim for a judgment on its ownership claim was subject to California statutes of limitation, we affirm that part of the district court's ruling. However, because the district court incorrectly declined to consider Roche's affirmative defense based on ownership, and because we conclude as a matter of law that Roche possesses an ownership interest in the patents-in-suit that deprives Stanford of standing, we vacate the district court's judgment of invalidity and remand with instructions to dismiss Stanford's action.

BACKGROUND

The patents-in-suit claim methods for quantifying Human Immunodeficiency Virus ("HIV")—the virus that causes Acquired Immunodeficiency Syndrome ("AIDS")—in human blood samples, and correlating those measurements to the therapeutic effectiveness of antiretroviral drugs. The claimed methods use the polymerase chain reaction ("PCR") to measure ribonucleic acid ("RNA") from HIV in the blood plasma of infected humans who are taking drugs such as zidovudine (AZT). PCR is a biochemical technique that enables measurement of relatively small quantities of nucleic acids by iteratively and exponentially "amplifying" a sample to detectable levels.

All three patents descend from a common parent application and share the same title: "Polymerase Chain Reaction Assays for Monitoring Antiviral

Therapy and Making Therapeutic Decisions in the Treatment of Acquired Immunodeficiency Syndrome." Three Stanford researchers—Mark Holodniy, Thomas Merigan, and David Katzenstein—are named inventors of all three patents; a fourth inventor, Michael Kozal, appears on the '705 patent.

The technology related to the patents-in-suit was developed in the late 1980s and early 1990s by researchers at Stanford and Cetus, a company where PCR techniques matured in the early 1980s. The collaborations between Stanford and Cetus included a series of written agreements. In 1988, Holodniy joined Merigan's laboratory at Stanford as a Research Fellow in the Department of Infectious Disease, and signed a "Copyright and Patent Agreement" ("CPA") that obligated Holodniy to assign his inventions to the university. J.A. 741-47. Holodniy had no prior experience with PCR techniques. In February 1989, Holodniy began regular visits to Cetus over several months to learn PCR and to develop a PCR-based assay for HIV. Holodniy signed a "Visitor's Confidentiality Agreement" ("VCA") with Cetus. Id. 1657-58. The VCA stated that Holodniy "will assign and do[es] hereby assign to CETUS, my right, title, and interest in each of the ideas, inventions and improvements" that Holodniy may devise "as a consequence of" his work at Cetus. Id. 1658.

During the same period, Cetus also collaborated with Merigan and Katzenstein to develop a separate HIV treatment. Merigan, Stanford, and Cetus signed multiple "Materials Transfer Agreements" that permitted Stanford to use certain PCR-related materials and information supplied by Cetus. Id. 1653-56. These agreements provided Cetus with

licenses to technology that Stanford created as a result of access to Cetus's materials. Id. 1655.

Eventually, Holodniy's research with Cetus produced an assay that used PCR to measure quantitatively the amount of plasma HIV RNA in samples from infected humans. After concluding his visits to Cetus and publishing his findings with Cetus coauthors, Holodniy worked with Merigan, Katzenstein, and others on clinical studies at Stanford that tested the new PCR assay with human patients taking antiretroviral drugs. The researchers determined that HIV RNA, measured through PCR, was a suitable "marker" of drug efficacy. These results formed the basis for the patents-in-suit.

In December 1991, Roche purchased Cetus's "PCR business," including its agreements with Stanford and its researchers, through an "Asset Purchase Agreement." Id. 3122, 3153-54. After this transaction, Roche began manufacturing HIV detection kits employing RNA assays. In May 1992, Stanford filed the patent application to which the patents-in-suit claim priority. The '730 patent issued on October 19, 1999; the '705 patent on January 7, 2003; and the '041 patent on October 31, 2006, after this lawsuit began. Stanford is the named assignee of all three patents.

Stanford received government funding for its HIV research through the National Institutes of Health ("NIH"). On June 24, 1992, Stanford filed an invention disclosure for the HIV RNA assay with the NIH. See id. 5091-93. On November 29, 1994, Stanford confirmed to the Government the grant of a "nonexclusive, nontransferable, irrevocable, paid-up license" under the parent application. Id. 5096. On

April 6, 1995, Stanford formally notified the Government that it elected to retain title to the inventions under the Bayh-Dole Act, 35 U.S.C. §§ 200-212. J.A. 5095. All three patents-in-suit contain the notation: "This invention was made with Government support under contracts AI27762-04 and AI27766-07 awarded by the National Institutes of Health. The Government has certain rights in this invention." E.g., '730 patent col.1 ll. 11-15.

On April 6, 2000, Luis Mejia, a Senior Licensing Associate at Stanford, offered a slide presentation at Roche that asserted Stanford's ownership of the HIV RNA assay invention and offered Roche an exclusive license to all patents descending from the parent application. J.A. 1201-18; Contract Op. at 1110. E-mail correspondence shows that as late as spring of 2004, Mejia and his Roche counterpart were negotiating possible license terms and contesting Roche's ownership rights in the patents. See Contract Op. at 1113.

Stanford filed suit against Roche in the Northern District of California on October 14, 2005, alleging that Roche's HIV detection kits infringe its patents. Roche answered and counterclaimed against Stanford, Merigan, and Holodniy, asserting, inter alia, that Stanford lacked standing to maintain the cause of action against Roche, that Roche possesses ownership, license, and/or shop rights to the patents through Roche's acquisition of Cetus's PCR assets, and that the asserted patent claims were invalid. Roche pleaded its ownership theory in three forms: as a declaratory judgment counterclaim, an affirmative defense, and a challenge to Stanford's standing to sue for infringement. Roche's First Am. Compl. 6-7, 13, 24.

The parties cross-moved for summary judgment on Roche's rights in the patents. Under Rule 8(c) of the Federal Rules of Civil Procedure, the district court construed Roche's pleading as a counterclaim but not an affirmative defense, reasoning that "Roche's claims of ownership of the patents and that Stanford lacks standing as the non-exclusive owner of the patents seek to expand Roche's current rights, and are properly viewed as counterclaims subject to the applicable statute of limitations." Contract Op. at 1112. The district court denied Roche's motion in full and granted Stanford's motion in part, finding that (1) Roche's ownership claims were barred by California statutes of limitation, laches, and the Bayh-Dole Act; (2) Roche's license claims failed because Stanford never consented to Roche's acquisition of Cetus's patent licenses; and (3) Roche lacked shop rights to the patents. Id. at 1124. Roche petitioned this court for a writ of mandamus to vacate the district court's ruling. We denied Roche's petition. In re Roche Molecular Sys., Inc., 516 F.3d 1003 (Fed. Cir. 2008).

After briefing and a Markman hearing, the district court then construed several claim terms. Bd. of Trs. v. Roche Molecular Sys., Inc., 528 F. Supp. 2d 967 (N.D. Cal. 2007). Roche then moved for summary judgment that the asserted claims were invalid. The district court granted the motion, holding all asserted claims obvious. Invalidity Op. at 1049.

Stanford appeals the judgment of invalidity and the district court's claim construction of "about 30 cycles"; Roche cross-appeals the judgment as to the parties' respective rights in the patents. We have jurisdiction under 28 U.S.C. § 1295(a)(1) (2006).

DISCUSSION

I. Propriety of Cross-Appeal

As a threshold matter, Stanford challenges the propriety of Roche's cross-appeal. Stanford argues that "the scope of [Roche's] cross-appeal includes only ownership" because Roche's license arguments "do not seek to modify the scope of the judgment below and, therefore, are not the proper subject of a cross-appeal." Stanford's Reply Br. 40. Stanford's characterization is incorrect. Although Roche mistakenly characterizes its ownership and license arguments as "alternative grounds" for affirmance, Roche's Principal Br. 2, 35, those arguments are not bases for invalidating the asserted claims. The district court's summary judgment of invalidity, which Stanford appeals, applies only to the asserted claims of the three patents-in-suit. Invalidity Op. at 1021. Roche's ownership and license arguments would establish Roche's rights to the patents as a whole, not only to specific claims. "It is . . . appropriate to file a cross-appeal when a party seeks to enlarge its own rights under the judgment or to lessen the rights of its adversary under the judgment. Thus, a party must file a cross-appeal when acceptance of the argument it wishes to advance would result in a reversal or modification of the judgment rather than an affirmance." Bailey v. Dart Container Corp., 292 F.3d 1360, 1362 (Fed. Cir. 2002) (citations omitted); see also Rivero v. City & County of San Francisco, 316 F.3d 857, 862 (9th Cir. 2002). Here, Roche's arguments would expand its rights under the judgment and, thus, are properly the subject of a cross-appeal.

II. The Parties' Patent Rights

Before the district court, Roche sought both to defeat Stanford's suit based on Stanford's alleged defective title and to obtain a judgment that it owned Holodniy's interest in the patents. The district court determined that the applicable California statutes of limitation and the doctrine of laches foreclosed Roche's counterclaim for a judgment of ownership, and that such determination was fatal to Roche's ownership and standing defenses. While we agree with the district court that the statutes of limitation preclude Roche from obtaining a judgment of ownership, we do not agree that such determination prevents Roche from asserting Stanford's lack of ownership of Holodniy's interest as a defense and a challenge to Stanford's standing to maintain its action against Roche.

"This court reviews the district court's grant or denial of summary judgment under the law of the regional circuit." MicroStrategy Inc. v. Business Objects, S.A., 429 F.3d 1344, 1349 (Fed. Cir. 2005). The Ninth Circuit "review[s] the district court's grant of summary judgment de novo, determining whether, viewing all evidence in the light most favorable to the nonmoving party, there are any genuine issues of material fact and whether the district court correctly applied the relevant substantive law." Kraus v. Presidio Trust Facilities Div., 572 F.3d 1039, 1043-44 (9th Cir. 2009).

Rule 8(c)(2) provides: "If a party mistakenly designates a defense as a counterclaim, or a counterclaim as a defense, the court must, if justice requires, treat the pleading as though it were correctly designated, and may impose terms for doing so." The

Federal Circuit "defers to the law of the regional circuits on matters of procedural law that do not implicate issues of patent law." Duro-Last, Inc. v. Custom Seal, Inc., 321 F.3d 1098, 1106 (Fed. Cir. 2003). In the Ninth Circuit, "a district court's decision[] with regard to the treatment of affirmative defenses is reviewed for an abuse of discretion." 389 Orange St. Partners v. Arnold, 179 F.3d 656, 664 (9th Cir. 1999).

We conclude that the district court abused its discretion by striking Roche's affirmative defense and refusing to adjudicate it on the merits. Rule 8(c)(2) generally applies if a party "mistakenly designates" its arguments. There is no indication that Roche erred when it pleaded ownership as both a declaratory judgment counterclaim and an affirmative defense, nor any reason why Roche could not have pleaded both to preserve its arguments. Cf. Dubied Mach. Co. v. Vt. Knitting Co., 739 F. Supp. 867, 871 n.3 (S.D.N.Y. 1990) ("It is permissible to label a response to a plaintiff's cause of action as both an affirmative defense and as a counterclaim."). The phrase "if justice requires" is not well defined. 389 Orange St., 179 F.3d at 664. But Rule 8(c)(2) generally favors defendants by construing responsive pleadings liberally to maximize the defendant's available legal theories. See Caldera v. Northrop Worldwide Aircraft Servs., 192 F.3d 962, 970 (Fed. Cir. 1999). Moreover, Rule 8(d)(2) permits a party to "set out two or more statements of a claim or defense alternatively or hypothetically." If a party pleads alternative statements, "the pleading is sufficient if any one of them is sufficient." Id.; see also MB Fin. Group, Inc. v. U.S. Postal Serv., 545 F.3d 814, 819 (9th Cir. 2008). Therefore, the district court was

obligated to consider Roche's counterclaim and defenses.

Under California law, "a defense may be raised at any time, even if the matter alleged would be barred by a statute of limitations if asserted as the basis for affirmative relief." Styne v. Stevens, 26 Cal. 4th 42, 51 (2001). The Supreme Court has repeatedly followed this distinction. Beach v. Ocwen Fed. Bank, 523 U.S. 410, 415-16 (1998) ("As we have said before, the object of a statute of limitation in keeping stale litigation out of the courts would be distorted if the statute were applied to bar an otherwise legitimate defense to a timely lawsuit . . . .") (quotation omitted); United States v. W. Pac. R.R. Co., 352 U.S. 59, 72 (1956) ("To use the statute of limitations to cut off the consideration of a particular defense in the case is quite foreign to the policy of preventing the commencement of stale litigation . . . . If this litigation is not stale, then no issue in it can be deemed stale."). Under these principles, the statutes of limitation do not preclude Roche's defense of ownership.

Stanford's assertion of laches and equitable estoppel also fail. Under California law, laches does not bar affirmative defenses. See Styne, 26 Cal. 4th at 52 ("[N]either the limitation of the statute nor the doctrine of laches will operate to bar the defense of the invalidity of the agreement upon the ground of fraud.") (citation omitted). Stanford has also not shown that Roche made any misrepresentations or concealed any facts about ownership needed for a valid claim of equitable estoppel. Simmons v. Ghaderi, 44 Cal. 4th 570, 584-85 (2008) (citations omitted).

Finally, and critically here, Roche asserted its ownership interest as a bar to Stanford's standing. It is well settled that questions of standing can be raised at any time and are not foreclosed by, or subject to, statutes of limitation. See Pandrol USA, LP v. Airboss Ry. Prods., 320 F.3d 1354, 1367 (Fed. Cir. 2003) (noting that "defendants' waiver of the defense of lack of patent ownership did not waive the defendants' ability to challenge the plaintiffs' standing to sue . . . at any stage of the litigation").

A. Chain of Title

1. The Agreements

"[T]he question of who owns the patent rights and on what terms typically is a question exclusively for state courts." Jim Arnold Corp. v. Hydrotech Sys., 109 F.3d 1567, 1572 (Fed. Cir. 1997); see also MyMail, Ltd. v. Am. Online, Inc., 476 F.3d 1372, 1376 (Fed. Cir. 2007). However, this rule has exceptions: the question of whether contractual language effects a present assignment of patent rights, or an agreement to assign rights in the future, is resolved by Federal Circuit law. "Although state law governs the interpretation of contracts generally, the question of whether a patent assignment clause creates an automatic assignment or merely an obligation to assign is intimately bound up with the question of standing in patent cases. We have accordingly treated it as a matter of federal law." DDB Techs., L.L.C. v. MLB Advanced Media, L.P., 517 F.3d 1284, 1290 (Fed. Cir. 2008) (citations omitted).

Holodniy signed multiple contracts defining his obligations to assign his invention rights. First, upon joining Stanford, Holodniy executed the CPA with

Stanford on June 28, 1988. J.A. 741. Holodniy signed as a "Fellow" in the Department of Infectious Disease. In the CPA, Holodniy acknowledges that Stanford enters into "Contracts or Grants" with third parties, such as the Government, and that he may "conceive or first actually reduce to practice" various inventions. Paragraph 2 of the CPA then recites: "I agree to assign or confirm in writing to Stanford and/or Sponsors that right, title and interest in . . . such inventions as required by Contracts or Grants." Id. (emphasis added).

We have held that the contract language "agree to assign" reflects a mere promise to assign rights in the future, not an immediate transfer of expectant interests. IpVenture, Inc. v. Prostar Computer, Inc., 503 F.3d 1324, 1327 (Fed. Cir. 2007) (interpreting "agree to assign" as "an agreement to assign," requiring a subsequent written instrument); see also Arachnid, Inc. v. Merit Indus., Inc., 939 F.2d 1574, 1580-81 (Fed. Cir. 1991) (holding that "will be assigned" does not create "a present assignment of an expectant interest"). Therefore, in the CPA, Holodniy agreed only to assign his invention rights to Stanford at an undetermined time. Additionally, Stanford's contemporary Administrative Guide to "Inventions, Patents, and Licensing" states: "Unlike industry and many other universities, Stanford's invention rights policy allows all rights to remain with the inventor if possible." J.A. 743. While Stanford might have gained certain equitable rights against Holodniy, see Arachnid, 939 F.3d at 1581 ("[A]n agreement to assign . . . may vest the promisee with equitable rights."), Stanford did not immediately gain title to Holodniy's inventions as a result of the CPA, nor at the time the inventions were created.

Next, when initiating his visits to Cetus, Holodniy signed the VCA on February 14, 1989. Paragraph 3 of the VCA recites: "I will assign and do hereby assign to CETUS, my right, title, and interest in each of the ideas, inventions and improvements." J.A. 1658 (emphasis added). In contrast to the CPA, the VCA's language of "do hereby assign" effected a present assignment of Holodniy's future inventions to Cetus. E.g., Speedplay, Inc. v. Bebop, Inc., 211 F.3d 1245, 1253 (Fed. Cir. 2000) (interpreting "shall belong" as a present assignment); FilmTec Corp. v. Allied-Signal, Inc., 939 F.2d 1568, 1572-73 (Fed. Cir. 1991). Therefore, Cetus immediately gained equitable title to Holodniy's inventions.

"Once the invention is made and an application for patent is filed, however, legal title to the rights accruing thereunder would be in the assignee . . . , and the assignor-inventor would have nothing remaining to assign." FilmTec, 939 F.2d at 1572. "Ordinarily, no further act would be required once an invention came into being; the transfer of title would occur by operation of law." Id. at 1573. Stanford filed the parent application to the patents-in-suit, Serial No. 07/883,327, on May 14, 1992, and there can be no dispute that Holodniy conceived his contribution to the invention by that date. Therefore, Cetus's equitable title converted to legal title no later than the parent application's filing date. Holodniy executed an assignment of his rights in the parent application to Stanford on May 4, 1995. J.A. 5070-71. However, because Cetus's legal title vested first, Holodniy no longer retained his rights, negating his subsequent assignment to Stanford during patent prosecution.

Stanford contends that there is a genuine factual dispute about whether the patents arose "as a consequence of" Holodniy's access to Cetus's facilities or information, as the VCA requires. We agree with the district court that "[t]his contention merits little discussion." Contract Op. at 1120. Stanford's various arguments boil down to assertions that the patented inventions were developed from nonconfidential information, or were conceived and reduced to practice after Holodniy ended his visits to Cetus. However, Holodniy testified that the collaboration provided him with "technical advice . . . from some of the Cetus scientists," J.A. 4509, information about PCR assays, id. 4514, and "the necessary reagents for the PCR reaction," id. 4523. Stanford also admitted in the parties' Joint Statement of Undisputed Facts that Holodniy received a PCR protocol, equipment for HIV RNA extraction, and access to equipment to perform reverse transcription of HIV RNA. J.A. 4790. It is undisputed that Holodniy took this information and material from Cetus and used them to develop the PCR assay for HIV RNA, and thus developed the inventions "as a consequence" of his access to Cetus. Even if Holodniy conceived and reduced to practice after departing Cetus, it was no later than May 14, 1992, and his research was directly related to the collaboration with Cetus. Thus, the chain of title to Holodniy's rights leads to Roche, leaving Stanford with defective title to the rights of all the inventors.

2. Bona Fide Purchaser

To overcome its defective chain of title, Stanford argues that it was a bona fide purchaser under 35 U.S.C § 261 (2006). Section 261 provides: "An assignment, grant or conveyance shall be void as

against any subsequent purchaser or mortgagee for a valuable consideration, without notice, unless it is recorded in the Patent and Trademark Office within three months from its date or prior to the date of such subsequent purchase or mortgage." "Generally, a bona fide purchaser is one who purchases legal title to property in good faith for valuable consideration, without notice of any other claim of interest in the property." Rhone-Poulenc Agro, S.A. v. DeKalb Genetics Corp., 284 F.3d 1323, 1329 (Fed. Cir. 2002) (collecting cases).

Stanford contends that it purchased Holodniy's rights through his 1995 assignment of the parent application for "good and valuable consideration," J.A. 5070, that Cetus and Roche never recorded their interests with the Patent and Trademark Office, and that Stanford received no notice of Holodniy's countervailing assignment to Cetus. However, Stanford's argument fails because there can be no genuine dispute that Stanford had at least constructive or inquiry notice of the VCA.

While "the bona fide purchaser defense to patent infringement is a matter of federal law," the doctrine draws upon common law principles. Rhone-Poulenc, 284 F.3d at 1328-30. "Notice" under § 261 can include constructive or inquiry notice, in addition to actual notice. See FilmTec, 939 F.2d at 1574 (noting that either actual or inquiry notice might defeat a bona fide purchaser defense). Therefore, Stanford's claim that it remained ignorant of the VCA until shortly before the current litigation is inconsequential. The CPA established an employment relationship between Holodniy and Stanford, and Holodniy's PCR work at Cetus related directly to his infectious disease research

at the university. J.A. 741. Moreover, Merigan, Holodniy's supervisor at Stanford, directed Holodniy to work with Cetus and himself executed Materials Transfer Agreements with Cetus that allocated intellectual property rights. See id. 4504-05. An organization can be charged with notice of its employees' assignments. See FilmTec, 939 F.2d at 1574 (noting that where a company founder signed away his patent rights, the company "may well be deemed to have had actual notice of an assignment"); see also Santillan v. Roman Catholic Bishop of Fresno, 163 Cal. App. 4th 4, 11 (Ct. App. 2008) ("For this purpose, there is no difference between constructive and actual notice. The rule applies to employees, who are agents of their employer.") (citations omitted); 3 Witkin Summary of California Law of Agency § 150 ("[A] corporation may be charged with notice of matters known to its employees."). The fact that Holodniy promised in the CPA to "not enter into any agreement creating copyright or patent obligations in conflict with this agreement" does not prevent imputation of notice to Stanford. See Restatement (Third) of Agency § 5.04 cmt. b (2006) ("Ordinarily, an agent's failure to disclose a material fact to a principal does not defeat imputation, nor does the fact that the agent's action otherwise constitutes a breach of a duty owed the principal.").

Stanford claims that Holodniy signed the VCA on his own behalf, not Stanford's. Although the VCA states that Holodniy was "[a]cting as a consultant and an independent contractor," the context of the VCA reveals that this refers to Holodniy's status as a consultant to Cetus, not Stanford. The VCA specified a limited time period for Holodniy's visits, restricted him from "perform[ing] consulting services" for other

companies, and listed his address as "Stanford University Medical Center, Division of Infectious Disease." J.A. 1657-58. Stanford also argues that there was no evidence that Holodniy "had authority to act as Stanford's agent in assigning patent rights." Stanford's Reply Br. 50. This contention misses the mark—Holodniy signed away his individual rights as an inventor, not Stanford's, while performing work for Stanford after promising to assign his rights to the university. Stanford identifies no other disputed facts that could establish its bona fide purchaser status, and thus cannot prevail on this theory.

3. The Bayh-Dole Act

The district court held in the alternative that the Bayh-Dole Act negated Holodniy's assignment to Cetus because it empowered Stanford to take complete title to the inventions. Congress passed the Bayh-Dole Act "to promote the utilization of inventions arising from federally supported research or development" and "to ensure that the Government obtains sufficient rights in federally supported inventions." 35 U.S.C. § 200 (2006). The Act allows the Government to take title to "subject inventions" under certain circumstances, id. §§ 202(a), 202(b), or the "contractor" universities or inventors to retain ownership if the Government does not, id. § 202(d).

Stanford contends—and the district court agreed—that Bayh-Dole allowed Stanford a "right of second refusal" to the patents after the Government refrained from exercising its rights. The court acknowledged our holding in Central Admixture Pharmacy Services, Inc. v. Advanced Cardiac Solutions, P.C. that when the Bayh-Dole Act's

provisions are violated, "the government can choose to take action; thus, title to the patent may be voidable. However, it is not void: title remains with the named inventors or their assignees. Nothing in the statute, regulations, or our caselaw indicates that title is automatically forfeited." 482 F.3d 1347, 1352-53 (Fed. Cir. 2007). Thus, the Act did not automatically void Holodniy's assignment to Cetus, and provided the Government with, at most, a discretionary option to his rights. The district court noted, however, that under 35 U.S.C. § 202(d), Holodniy, as an inventor, could keep title to his inventions only "[i]f a contractor does not elect to retain title to a subject invention." On appeal, Stanford insists that Holodniy's rights were "contingent" upon his CPA obligations to assign them to Stanford, and that Stanford's election of title in 1995 gave it all patent rights. Stanford's Reply Br. 47.

We are unconvinced of Stanford's interpretation of the Bayh-Dole Act in this case. Stanford identifies no authorities or reasons why its election of title under Bayh-Dole had the power to void any prior, otherwise valid assignments of patent rights. Stanford was entitled to claim whatever rights were still available after the Government declined to exercise its option, including the rights of co-inventors Merigan, Katzenstein, and Kozal. However, Holodniy transferred his rights to Cetus more than six years before Stanford formally notified the Government of its election of title. As previously noted, Stanford's invention rights policy "allow[ed] all rights to remain with the inventor if possible," J.A. 743, which supports the conclusion that Holodniy still possessed rights at the time he signed the VCA with Cetus. Just as we explained that Bayh-Dole does not automatically void ab initio the inventors' rights in government-funded

inventions, Cent. Admixture, 482 F.3d at 1352-53, we see no reason why the Act voids prior contractual transfers of rights.[4]

The ownership dispute in University of Pittsburgh v. Townsend is instructive. 2007 U.S. Dist. LEXIS 56860 (E.D. Tenn. Aug. 3, 2007), aff'd, 542 F.3d 513 (6th Cir. 2008). There, the University of Pittsburgh sought patent rights from Townsend, the inventor. The University employed Townsend and claimed all rights in his inventions, but Townsend maintained simultaneous ties with a private company, CTI. After inventing a medical scanner, Townsend assigned his rights exclusively to CTI. Critically, the University then formally elected title under the Bayh-Dole Act. Before the district court, the University argued that this election voided Townsend's earlier assignment. To support this argument, the University cited the Northern District of California's analysis of Bayh-Dole in the current case between Stanford and Roche. 2007 U.S. Dist. LEXIS 56860, at *59-61. The Townsend district court rejected this position, noting that "the University's ostensible exercise of its right to title . . . occurred after Dr. Townsend's assignment to CTI." Id. at *60-61. The University's Bayh-Dole election did not give it superior title, nor prevent Pennsylvania statutes of limitation from barring the University's contract and tort claims. The Sixth Circuit noted the University's use of Bayh-Dole, but nevertheless affirmed the statutes of limitation holding. 542 F.3d at

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[4] We express no opinion as to whether Holodniy's execution of the VCA violated any provisions of the Bayh-Dole Act, or whether the Act provides the Government or Stanford some other legal recourse to recover Holodniy's rights. Cf. Cent. Admixture, 482 F.3d at 1353.

520 & n.1. This outcome is consistent with our understanding that claiming title under Bayh-Dole does not override prior assignments.

Regardless of any state law contractual obligations between an academic and his university, "the primary purpose of the Bayh-Dole Act is to regulate relationships of small business and nonprofit grantees with the Government, not between grantees and the inventors who work for them." Fenn v. Yale Univ., 393 F. Supp. 2d 133, 141-42 (D. Conn. 2004). Therefore, in this case, the Bayh-Dole statutory scheme did not automatically void the patent rights that Cetus received from Holodniy.

4. California Business and Professions Code § 16600

Under California law, "every contract by which anyone is restrained from engaging in a lawful profession, trade, or business of any kind is to that extent void." Cal. Bus. & Prof. Code § 16600 (2009). Stanford argues that section 16600 voids the VCA because Holodniy conceived the patented invention after departing Cetus, and the VCA violates public policy if it encompasses inventions conceived after employment terminates. Stanford also contends that once Holodniy's research was published, it became public information, and that Roche's interpretation of the VCA would prevent Holodniy from using this information in his later clinical studies.

We find no merit in Stanford's arguments. By the plain language of section 16600, only those contracts that prevent "engaging in a lawful profession, trade or business of any kind" are void. Stanford provides no evidence that the VCA restrained Holodniy from

engaging in any profession. Indeed, the record shows that Holodniy freely continued his HIV research at Stanford, publishing articles and using the knowledge he obtained from Cetus to further the science behind the patents in suit. Nor does Stanford explain how Holodniy's assignment of his rights to Cetus prohibited Holodniy from using any public information in his later research. Moreover, California courts apply section 16600 to employment restrictions on departing employees, not to patent assignments. See Thompson v. Impaxx, Inc., 113 Cal. App. 4th 1425, 1429 (Ct. App. 2003); D'Sa v. Playhut, 85 Cal. App. 4th 927, 934-35 (Ct. App. 2000).

B. Statutes of Limitation

Roche's counterclaim requests a declaratory judgment of ownership of the patents, which is generally a matter of state law. The district court had supplemental jurisdiction over this claim under 28 U.S.C. § 1367 (2006). While the district court expressed some doubt as to which statutes of limitation apply to state claims in federal court under supplemental jurisdiction, Contract Op. at 1112, other circuits have noted—and the parties here do not dispute—that state statutes of limitation apply. See Bouton v. BMW of N. Am., 29 F.3d 103, 110 (3d Cir. 1994) ("The Rules of Decision Act arguably is also the source of authority for applying state statute of limitations to state law claims brought under supplemental jurisdiction."); see also James William Moore et. al, Moore's Manual: Federal Practice and Procedure § 11.64[5] (2009) ("[W]hen the court has supplemental jurisdiction over a state-law claim, the state statute of limitations and related principles of tolling and relation back apply to the actions.").

Under California law, "the period of limitations applicable to ordinary actions at law and suits in equity should be applied in like manner to actions for declaratory relief." Maguire v. Hibernia Sav. & Loan Soc., 23 Cal. 2d 719, 734 (1944). The parties identified two relevant statutes of limitation, both imposing a four-year deadline. California Code of Civil Procedure § 337(1) (2009) provides that "[a]n action upon any contract, obligation or liability founded upon an instrument in writing" must be brought within four years. While there is no contract between Roche and Stanford, Roche's claim to Holodniy's patent rights is based on a written agreement, the VCA. Alternatively, California Code of Civil Procedure § 343 (2009) applies a residuary four-year limitation period to all causes of action that do not fall under specific statutes of limitation.[2] Under either statute, Roche's claim is subject to a four-year limitation period.

In California, "[i]t is elementary that a statute of limitations does not begin to run until the cause of action accrues. Equally basic is that a cause of action does not accrue 'until the party owning it is entitled to begin and prosecute an action thereon,' that is, not until 'the last element essential to the cause of action' occurs." Spear v. Cal. State Auto. Ass'n, 2 Cal. 4th 1035, 1040 (1992) (citations omitted). "A contract cause of action does not accrue until the contract has been breached." Id. at 1042. For a declaratory judgment action, the limitations period begins when the

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[2] Additionally, § 338(c) applies a three-year limitation to actions "for taking, detaining, or injuring any goods or chattels, including actions for the specific recovery of personal property." While patents have the attributes of personal property, 35 U.S.C. § 261, Stanford does not argue on appeal that § 338(c) applies.

corresponding claim for damages or injunction accrues. Howard Jarvis Taxpayers Ass'n v. City of La Habra, 25 Cal. 4th 809, 821 (2001). However, the "discovery rule" mitigates the accrual of claims. "'The discovery rule 'postpones accrual of a cause of action until the plaintiff discovers, or has reason to discover, the cause of action,'" E-Fab, Inc. v. Accountants, Inc. Servs., 153 Cal. App. 4th 1308, 1318 (Ct. App. 2007) (citation omitted), and "the statute of limitations begins to run when the plaintiff has reason to suspect an injury and some wrongful cause," Fox v. Ethicon Endo-Surgery, Inc., 35 Cal. 4th 797, 803 (2005). "While resolution of the statute of limitations issue is normally a question of fact, where the uncontradicted facts established through discovery are susceptible of only one legitimate inference, summary judgment is proper." Jolly v. Eli Lilly & Co., 44 Cal. 3d 1103, 1112 (1988).

The district court correctly concluded, based on Stanford's undisputed evidence, that Roche's claim accrued no later than April 2000. On April 6, 2000, Luis Mejia, a Stanford employee, conducted a slide presentation at Roche that asserted Stanford's ownership of the HIV RNA assay invention and offered Roche a license to all relevant patents. J.A. 1201-18; Contract Op. at 1110. Mejia's presentation occurred more than four years before Stanford filed its complaint on October 14, 2005. See Sidney v. Superior Court, 198 Cal. App. 3d 710, 714-15 (Ct. App. 1988) (noting that "a statute of limitations is suspended by the filing of the original complaint" (citation omitted)). Mejia's slide presentation begins with Stanford's offer to license the invention entitled "PCR Assays for Monitoring Antiviral Therapy and Making Therapeutic Decisions in the Treatment of AIDS," which is the title common to all three patents-in-suit. J.A. 1201. The

presentation then describes Holodniy's contribution to the conception of the invention, and notes that the '730 patent issued in 1999. Most importantly, the presentation states that "[c]ontinuations based on the same application 'family' remain pending" and offers Roche a license that "would include rights to patents that may issue based on pending applications from the same patent 'family.'" Id. 1210, 1216 (emphases added). Therefore, Mejia's slides put Roche on notice that Stanford claimed ownership of Holodniy's work, that Stanford had patented the invention related to the Holodniy-Cetus collaboration, that Stanford continued to file related patent applications, and that Stanford expected Roche to take a license to current and future patents. These statements directly contradicted Roche's claim that it owns all of Holodniy's rights to any "ideas, inventions and improvements thereof" under the VCA. Id. 1658. Thus, Roche's ownership claim accrued upon receipt of the Mejia presentation.

Roche does not dispute the contents of the presentation, but argues that a cause of action for patent ownership cannot accrue until each patent issues. The Mejia presentation occurred before the filing dates of the applications for the '705 and '041 patents (February 13, 2001 and December 16, 2002, respectively). Roche cites Stark v. Advanced Magnetics, Inc., where this court stated that because "each patent is a separate chose in action," laches for an inventorship correction claim does not run until each patent issues. 29 F.3d 1570, 1576 (Fed. Cir. 1994). However, Stark relied on the facts that, at the time the case was decided, pending patent applications were secret, and the party challenging inventorship lacked actual knowledge of the applications. Id. Here,

however, Roche had explicit notice that Stanford intended to secure additional patents to the same subject matter. Roche also had other constructive notice of the related patents because the application resulting in the '705 patent, No. 09/782,971, was published on August 30, 2001, more than four years before Stanford filed suit. Moreover, the case that Stark cites for the proposition that each patent is a separate action, Meyers v. Brooks Shoe, Inc., 912 F.2d 1459 (Fed. Cir. 1990), discusses laches for a patentee to bring an infringement suit. This is logical because "suit can not be brought for infringement of a patent that has not issued." Amgen, Inc. v. Genetics Inst., 98 F.3d 1328, 1332 (Fed. Cir. 1996). However, Meyers does not say that if an alleged co-owner claims ownership of an invention, and knows that a related patent application is forthcoming, its cause of action under state law does not accrue until patent issuance. Cf. FilmTec, 939 F.2d at 1572-73 (noting that legal title can transfer "[o]nce the invention is made and an application for patent is filed").

Roche also claims that our holding in DDB Technologies, L.L.C. v. MLB Advanced Media, L.P. precludes application of state statutes of limitation to patent ownership claims. 517 F.3d 1284 (Fed. Cir. 2008). In DDB, we determined that an inventor's contract with an employer was an "automatic assignment" of future patent rights. Because the assignment was automatic, the plaintiff's statute of limitations, waiver, and estoppel challenges to the patent assignment had "no merit." Id. at 1290. However, we affirmed this result only because the district court held that Texas law prevents an assignor from urging estoppel or waiver against an assignee. See DDB Techs., L.L.C. v. MLB Advanced Media, L.P.,

465 F. Supp. 2d 657, 669 (W.D. Tex. 2006); see also Univ. of Tex. Med. Branch v. Allan, 777 S.W.2d 450, 453 (Ct. App. Tex. 1989). In the present case, Roche has not identified, nor can we find, any similar rule under California law. We thus conclude that Roche's counterclaim for a judgment of ownership of the '730, '705, and '430 patents is time-barred by statutes of limitation, and the district court correctly dismissed Roche's claim for a judgment of ownership on that ground. We need not reach the district court's conclusion that laches also applies to Roche's counterclaim.

C. Stanford's Standing

Notwithstanding the running of the statutes of limitation against Roche's claim for a judgment of ownership, Stanford's inability to establish that it possessed Holodniy's interest in the patents-in-suit defeats its right to assert its cause of action against Roche. It is well settled that "all co-owners normally must join as plaintiffs in an infringement suit." Int'l Nutrition Co. v. Horphag Research Ltd., 257 F.3d 1324, 1331 (Fed. Cir. 2001) (finding lack of standing where defendant co-owner did not voluntarily join); see also Isr. Bio-Eng'g Project v. Amgen Inc., 475 F.3d 1256, 1264-65 (Fed. Cir. 2007) ("Absent the voluntary joinder of all co-owners of a patent, a co-owner acting alone will lack standing."); Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1467 (Fed. Cir. 1998) ("An action for infringement must join as plaintiffs all co-owners."). Roche asserted its ownership claim not only as a counterclaim seeking a judgment of ownership of Holodniy's interests, but also as an affirmative defense and a challenge to Stanford's standing to assert claims of infringement against

Roche. While Roche's failure to timely seek a judgment of ownership defeats its counterclaim, it does not alter the fact that Stanford cannot establish ownership of Holodniy's interest and lacks standing to assert its claims of infringement against Roche. Thus, the district court lacked jurisdiction over Stanford's infringement claim and should not have addressed the validity of the patents. See Morrow v. Microsoft Corp., 499 F.3d 1332, 1344 (Fed. Cir. 2007). The district court's grant of summary judgment of invalidity is therefore vacated, and the case is remanded with instructions to dismiss Stanford's claim for lack of standing.

CONCLUSION

For the foregoing reasons, we affirm the district court's dismissal of Roche's ownership counterclaim, vacate the judgment that the asserted patent claims were invalid for obviousness, and remand with instructions to dismiss Stanford's claim.

AFFIRMED-IN-PART, VACATED-IN-PART, AND REMANDED

COSTS

Each party shall bear its own costs.

APPENDIX B

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

No. C 05-04158 MHP

[Filed April 16, 2007]

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiff,

v.

ROCHE MOLECULAR SYSTEMS, INC.; ROCHE DIAGNOSTICS CORPORATION; ROCHE DIAGNOSTICS OPERATIONS, INC.; and ROCHE DIAGNOSTIC SYSTEMS, INC.,

Defendants.

ROCHE MOLECULAR SYSTEMS, INC.; ROCHE DIAGNOSTICS CORPORATION; and ROCHE DIAGNOSTICS OPERATIONS, INC.,

Counterclaimants,

v.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY; THOMAS

MERIGAN; and MARK HOLODNIY,)
)
Counterclaim Defendants.)
)

MEMORANDUM & ORDER
Cross-Motions for Summary Judgment

On October 14, 2005 plaintiff Board of Trustees of the Leland Stanford Junior University ("plaintiff" or "Stanford") brought this action against Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc., and Roche Diagnostic Systems, Inc.[1] (collectively "defendants," "counterclaimants" or "Roche") alleging infringement of U.S. Patents Nos. 5,968,730 ("the '730 patent") and 6,503,705 ("the '705 patent"). On November 17, 2005 Roche filed a counterclaim against Stanford, naming Dr. Thomas Merigan ("Merigan") as an additional counterclaim defendant. In June 2006, Roche amended its counterclaim without objection to add Dr. Mark Holodniy ("Holodniy") as a counterclaim defendant. Although counterclaimants assert fourteen counterclaims, the relevant counterclaims to this motion are Counterclaim Four, for Declaratory Judgment of Ownership of the '730 and '705 patents against Stanford, and Counterclaim Six, for Declaratory Judgment of License to the '730 and '705 patents against Stanford. These counterclaims have also been pled as affirmative defenses. Now before the court are the parties' cross-motions for summary

[1] Roche Diagnostic Systems, Inc. was dismissed as a defendant without prejudice by stipulation of the parties entered on November 17, 2005.

judgment on Roche's ownership and license claims.[2] The court has considered the parties' arguments fully, and for the reasons set forth below, the court rules as follows.

BACKGROUND

This patent dispute concerns the application of Polymerase Chain Reaction (PCR) technology in the context of HIV/AIDS research. Stanford currently owns two patents titled "Polymerase Chain Reaction Assays for Monitoring Antiviral Therapy and Making Therapeutic Decisions in the Treatment of Acquired Immunodeficiency Syndrome." The '705 patent is a continuation of the '730 patent. The patents involve correlating measurements of HIV nucleic acids obtained via a PCR assay with determining whether or not a therapy is effective. It is undisputed that Stanford developed the PCR assay disclosed in its patents after working with Cetus Corporation ("Cetus"), which later sold its PCR assets and business to Roche. The extent and legal effect of the collaboration between Stanford and Cetus is the subject of the instant cross-motions for summary judgment.

Counterclaim defendant Merigan joined Cetus' Scientific Advisory Board in 1979. Merigan Dep. at 73:10–14, 91:6–92:7, 95:19–99:1. At that time, Merigan was a Professor of Medicine at Stanford whose

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[2] Although Stanford discusses additional patents in its "patent family," this motion is limited to claims involving the '730 and '705 patents. In addition, Roche's claims based on inventorship and inequitable conduct are not at issue in this motion.

research focused on infectious diseases. Id. at 24:3–25:14. Cetus sought Merigan's expertise in furtherance of obtaining regulatory approval for the drug Interleukin-2 ("IL-2"), the development of which was Cetus' main research focus at that time. Id. at 95:19–98:5; White Dep. at 53:22–54:8, 61:1–5, 63:14–24. As part of Merigan's relationship with Cetus, Cetus and Merigan entered into formal consulting agreements signed in 1980, 1984 and 1991. Rhyu Dec., Exhs. 351, 352, 356 & 369. The agreements recognized Merigan's obligations to Stanford. Rhyu Dec., Exhs. 351 ¶ 3(a), 352 ¶ 3(a), 356 ¶ 3, 369 ¶ 4.

PCR was initially developed by Cetus scientists in the mid-1980s. Holodniy Dep. at 84:19–85:11. Through the use of PCR, scientists are able to make billions of copies of specific sequences of DNA from a small number of starting molecules. Cetus scientist Kary Mullis received the Nobel Prize in chemistry for his work developing PCR. Id. at 85:12–21. In 1985, Cetus began looking for ways to use PCR to detect and quantify the presence of HIV in blood. Sninsky Dec. ¶¶ 5–9; see also Kwok Dep. at 46:8–15. Meanwhile, Merigan had become focused on the treatment of AIDS in his own research. Merigan Dep. at 25:20–27:10. Merigan helped establish Stanford's Center for AIDS Research, and became the Director of the Center in the late 1980s. Id. at 25:20–27:10.

The collaboration between Cetus and Stanford concerning the use of PCR in HIV/AIDS research began in 1988, when the two entities were involved in a clinical trial exploring the efficacy of using IL-2 to treat AIDS patients. Groves Dec. ¶ 4; Schwartz Dep. at 48:20–50:20; Holodniy Dep. at 18:16–23. Merigan and Dr. David Schwartz headed the Stanford team. During

his time with Cetus, Merigan entered into a number of Materials Transfer Agreements establishing Merigan's right to use Cetus' proprietary materials and information in exchange for a non-exclusive, royalty-free license to Cetus for any intellectual property developed as a result of the MTA. Chiang Dec., Exhs. 4–6; Ostrach Dep. at 91:5–94:25.

As part of the clinical trial, the Cetus team used PCR to quantitate the HIV levels of the participating patents. Groves Dec. ¶ 5; Schwartz Dep. at 49:24–50:13. [2]The patient samples were provided by Merigan and Schwartz so that Cetus could perform its PCR assays. Groves Dep. at 45:24–47:10; Merigan Dep. at 62:17–64:13. Cetus shared the results of the PCR testing with Merigan and Schwartz throughout the summer and fall of 1988. Groves Dec. ¶¶ 6–8, Exh. 1; Groves Dep. at 45:6–46:23. Stanford subsequently sought to independently reproduce the results of Cetus' PCR testing, and Drs. Merigan and Schwartz requested "a written copy of the Cetus protocol for extraction, amplification and quantitation of HIV DNA" using PCR by letter dated November 7, 1988. Chiang Dec., Exh. 8; Merigan Dep. at 281:13–283:8.

The following month, Cetus attempted to enter into an additional Materials Transfer Agreement with Stanford, Merigan, and Schwartz via letter dated December 19, 1988 ("the 1988 MTA"). Chiang Dec., Exh. 10; Groves Dec. ¶ 10; Merigan Dep. at 288:17–291:8. The MTA was signed in February 1989. Chiang Dec., Exh. 10. Pursuant to the MTA, Cetus would provide Stanford with "certain research substances and know-how" in exchange for certain concessions on the part of Stanford. Chiang Dec., Exh. 10; Groves Dec. ¶ 10; Ostrach Dep. at 90:16–91:3,

Schwartz Dep. at 44:24–46:3, 60:19–61:9. Specifically, the MTA provides that Stanford will (1) "inform CETUS, in confidence, of research results related to the Material . . . [and] CETUS shall be free to use such data and information for any purpose;" (2) identify Cetus' role in the development of any "invention . . . that may be commercially useful" when disclosing the invention to Stanford's patent agent; and (3) supply Cetus with a copy of any such disclosures for Cetus' evaluation purposes. Chiang Dec., Exh. 10 ¶¶ 2, 7 & 8. The MTA further provided that Cetus was given "the first option to an exclusive license, at a reasonable royalty to be negotiated in good faith . . ., or at CETUS' option, a nonexclusive license." Id. at ¶ 8. Stanford asserts that there is no evidence that any materials were actually transferred to Schwartz or Merigan pursuant to this agreement. Merigan Dep. at 66:5–7, 68:4–69:6, 290:24–291:8. Merigan testified that the Cetus PCR tests on Stanford samples conducted in Fall 1988 were only "semiquantitative" and would require "considerable effort" to improve them before they could provide clinically useful information. Id. at 271:21–273:25. Schwartz likewise testified that the Cetus results were "inadequate for quantitation." Schwartz Dep. at 99:21–105:22.

Within a few weeks of the 1988 MTA agreement, counterclaim defendant Mark Holodniy, then a fellow in Stanford's Division of Infectious Diseases, began spending time at Cetus in order to explore the use of PCR techniques in his work. Holodniy had joined Stanford in July 1988 as part of a fellowship program that involved "working on HIV trials with antiretroviral drugs" and "develop[ing] some sort of marker to be able to assess the effectiveness of therapy." Holodniy Dep. at 103:24–104:18. Holodniy

had no previous PCR experience prior to joining Stanford. Id. at 83:9–85:4. Holodniy began working in Merigan's lab in October 1988, working to "find a molecular based test to measure the effectiveness of antiviral treatments." Id. at 113:12–114:1; Merigan Dep. at 78:3–79:1, 80:10–81:11. Holodniy spent several months at Stanford doing research and experiments related to PCR. Holodniy Dec. ¶¶ 7 & 8; Chiang Dec., Exh. 5 at 4; Holodniy Dep. at 139:16–140:10, 143:2–144:16, 146:13 23. In February 1989, after Merigan suggested that Holodniy spend time at Cetus to develop a better assay for quantitating the level of nucleic acids, Holodniy began commuting daily to Cetus. Holodniy Dec. ¶ 9; Chiang Dec., Exh. 9 at 5–6; Holodniy Dep. at 13:24–14:5. According to Holodniy's deposition testimony, his role in working at Cetus was "to develop an assay at Stanford that [they] could use to monitor treatment" after "discussions with Cetus scientists about the feasibility of establishing a quantitative assay." Id. at 152:20–153:11. Holodniy was assigned a lab bench in Cetus' Clinical Group, and had access to Cetus personnel, materials, and equipment. Id. at 31:17–25, 169:12–17, 182:21–184:1, 250:3–15; Groves Dec. ¶¶ 10 & 11.

At the time Holodniy began working at Cetus in February 1989, he signed a Visitor Confidentiality Agreement (VCA). Groves Dep. at 99:5–102:7; Holodniy Dep. at 155:8–18; Groves Dec. ¶ 11. The VCA provided:

> If, as a consequence of my access to CETUS' facilities or information, I conceive of or make, alone or with others, ideas, inventions and improvements thereof or know-how related thereto that relate in any manner to the actual

> or anticipated business of CETUS, I will assign and do hereby assign to CETUS, my right, title, and interest in each of the ideas, inventions and improvements thereof described in this paragraph.

Chiang Dec., Exh. 11 ¶ 3. Holodniy spent approximately nine months working at Cetus, receiving technical information from Cetus scientists and proprietary physical materials from Cetus. Joint Statement of Undisputed Facts ("JSUF") ¶¶ 9, 14–17, 19–21, 23–25, 27, 28, 30.

By fall 1989, an assay for quantitating HIV RNA using PCR was developed at Cetus that was comprised of five steps: (1) extraction of the HIV RNA from serum or plasma ("extraction"), (2) copying the single-stranded HIV RNA into a double-stranded DNA molecule ("reverse transcription"), (3) using PCR to make millions of copies of the DNA using primers developed by Cetus ("amplification"), (4) detecting the amplified DNA using a DNA probe ("detection"), and (5) generation of a standard curve used to calculate the amount of virus in a patient's blood using a cRNA standard ("quantitation"). Chiang Dec., Exh. 9; Holodniy Dep. at 23:23–24:7, 63:3–71:2; Holodniy Dec. ¶ 16.

At the time the assay was developed, Holodniy had no experience creating or using standards such as the cRNA standard for quantitation. Holodniy Dep. at 161:10–162:20. Accordingly, Holodniy sought the assistance of Cetus scientist Alice Wang to develop the quantitation portion of the assay. Id. at 72:25–74:6, 161:10–162:20, 399:13–24. The cRNA standard was developed by Clayton Casipit, who worked in Wang's

lab. Chiang Dec., Exh. 15; Casipit Dep. at 17:3–18:24. The cRNA standard was provided to Holodniy in October 1989. Chiang Dec., Exh. 15 at CD 524; Holodniy Dep. at 72:7–19, 261:11–25. Holodniy has testified that he had never performed any of the five steps comprising the assay prior to working at Cetus. Id. at 155:23–157:24, 173:3–25, 254:2–262:3.

In December 1989, Holodniy requested permission from Cetus to publish the HIV RNA Quantitation Assay in two abstracts, one to be presented at the UCLA Keystone Symposium on Molecular and Cell Biology and the other to be presented at the Sixth International AIDS Conference in San Francisco. Chiang Dec., Exh. 17; Holodniy Dec. ¶¶ 19, 21, 22; Rhyu Dec., Exhs. 35 & 41. Cetus granted permission after Holodniy added the names of Wang, Casipit and Dr. Michael Konrad, another Cetus scientist, to the abstract. Chiang Dec., Exhs. 17 & 18. Cetus also requested that the information in the abstract be kept confidential until publication, as some of the technology was the subject of a pending patent application. Chiang Dec., Exh. 18. The abstract, titled "Quantitation of HIV-1 in Serum and Correlation with Disease Status Using the Polymerase Chain Reaction," concludes that the authors have demonstrated that HIV viral RNA can be detected and quantified in patient serum and that such quantitation "may be a useful marker for disease progression or monitoring antiviral therapy." Chiang Dec., Exh. 20. The abstract was presented at the UCLA Symposium in March or April 1990. Chiang Dec., Exh. 21 at RMS 544; Holodniy Dec. ¶ 19.

In January 1990, Konrad submitted an invention disclosure on behalf of Holodniy titled "Quantitation of

HIV-1 viral RNA in human serum utilizing an in vitro generated internal standard for coamplification and an enzyme linked affinity assay for detection." Chiang Dec., Exh. 21; Holodniy Dep. at 275:1–278:4; Holodniy Dec. ¶ 20. The disclosure form includes a copy of the UCLA Abstract, references Holodniy's personal notebook, and indicates that the cRNA standard used in the invention was designed and constructed by Cetus personnel. Chiang Dec., Exh. 21. Holodniy testified to his belief that Cetus gave him the form out of concern for Cetus' interest in the subject matter of the invention disclosure. Holodniy Dep. at 277:10–278:1, 278:13–21. The Cetus patent committee gave the invention disclosure a ranking of "5," which is the committee's lowest possible ranking.[3] Rhyu Dec., Exh. 518 at RMS 6456, 6460. Accordingly, Cetus never filed a patent application related to that disclosure or asked Holodniy to cooperate in the filing of a patent. Holodniy Dec. ¶ 20.

In April 1991, the Journal of Infectious Diseases published an article titled "Detection and Quantification of Human Immunodeficiency Virus RNA in Patient Serum by Use of the Polymerase Chain Reaction" ("the JID Article"), with Holodniy as

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[3] Under Cetus' ranking system, an invention disclosure given a ranking of "1" was "given the highest priority for action by the law department." White Dep. at 248:6–11. The system's lower rankings could mean a variety of things, including "that the committee thought the material had already been covered," that "there was not enough information to make a decision . . . or something to be revisited," that the disclosure should be published, or that the disclosure should be retained as confidential. Id. at 248:23–249:6. A ranking of "5" did not necessarily mean freedom to publish. Id. at 249:6–8.

the lead author and Merigan, Wang, Casipit, and other scientists from both Stanford and Cetus listed as co-authors. Chiang Dec., Exh. 22; Holodniy Dec. ¶ 22. The article describes the five steps of the PCR assay developed by Holodniy at Cetus. Chiang Dec., Exh. 22 at RMS 01468–68. The article further states that "[t]hese results demonstrate that HIV RNA in serum can be detected and quantitated by reverse transcription, PCR, and a nonisotopic enzyme-linked affinity assay." Id. at RMS 01470–71. In addition, the article states that HIV RNA may be recovered and used more efficiently from plasma. Id. at RMS 01471. Regarding applications of the PCR assay, the article states that "[q]uantitation of infectious HIV RNA in cell-free serum by PCR may be useful as a marker for disease progression or in monitoring anti-viral therapy," and that "[s]erum PCR may provide an additional marker of disease progression and drug efficacy that could improve our ability to monitor the course of HIV infection." Id. Following this latter statement, the article concludes that "[f]urther studies will be necessary to validate this approach." Id. Cetus approved the manuscript of the JID Article prior to publication. Rhyu Dec., Exh. 39; Holodniy Dec. ¶ 22. Cetus had also approved the publication of a separate article in 1991 describing the assay and the inhibition of the PCR reactions by heparin. Rhyu Dec., Exh. 13.

In July 1990, Holodniy began experiments at Stanford attempting to correlate the detection of HIV nucleic acid levels via the PCR assays with the effectiveness of HIV treatment. Holodniy Dec. ¶¶ 25 & 27. According to Holodniy, additional work was needed regarding the PCR assay published in the JID article before its usefulness in ascertaining the efficacy of HIV treatment could be established. Id. at ¶¶ 27 & 28.

Holodniy worked with Merigan and Katzenstein on the experiments, using patient samples provided by Dr. Dennis Israelski. Id. at ¶ 29. Cetus was not involved in these experiments. Id. Holodniy, Merigan and Katzenstein worked on the experiments through the summer and winter of 1990 before demonstrating a correlation between HIV levels and effectiveness of treatment sometime during the first half of 1991. Id. These experiments formed the basis of a manuscript submitted by Holodniy, Merigan, Katzenstein and Israelski to the Journal of Clinical Investigation in May 1991 and published in November of that year titled "Reduction in Plasma Human Immunodeficiency Virus Ribonucleic Acid after Dideoxynucleoside Therapy as Determined by the Polymerase Chain Reaction" ("the JCI Article"). Rhyu Dec., Exh. 46; Holodniy Dec. ¶ 30. Dr. Sninsky, the head of the PCR division at Cetus, testified that he read the JCI article while he was at Cetus, and that he "generally read papers on HIV," but could not recall specifically when he read the JCI article. Sninsky Dep. at 226:16–227:9.

On May 14, 1992, Stanford submitted the parent application for the patent family that would include the '730 and '705 patents, initially listing only Merigan and Dr. Michael Kozal as inventors. According to Stanford, the work published in the JCI article formed the basis for this patent application. Holodniy Dec. ¶ 30. In November 1992, Stanford petitioned to correct inventorship to add Holodniy and Katzenstein as joint inventors. Chiang Dec., Exh. 31. Holodniy's inventive contribution was identified as principally concerning "quantitation of HIV RNA in plasma of AIDS patients." Chiang Dec., Exh. 29 ¶ 7. The petition further noted that Holodniy's inventive contribution occurred during his time as a research fellow in

Stanford's Division of Infectious Disease. Id. In a letter from Holodniy to Stanford's patent counsel regarding Holodniy's involvement in patent application, Holodniy identifies two major contributions on his part. First, Holodniy states that the section of the application beginning "PCR assay of plasma HIV RNA" is a "body of work published in the Journal of Infectious Diseases." Chiang Dec., Exh. 26 at PENNIE 1381. Holodniy identifies his "other major contribution" as "work which demonstrates a reduction in plasma HIV RNA after dideoxynucleoside therapy is determined by the polymerase chain reaction," referencing the JCI article. Id. at PENNIE 1382. Holodniy identifies this contribution as "crucial to the invention because it demonstrates the utility of using plasma HIV RNA as a marker for antiretroviral therapy." Id.

The '730 patent issued on October 19, 1999. The '705 patent, a continuation of the '730 patent relying on a substantively identical specification, issued on January 7, 2003. Table 1 and Figures 1–3 of the JCI article correspond to Table 1 and Figures 1–3 of the '730 and '705 patents. The "parent" application to all of the Merigan patents became publicly available in 1997. Mejia Dec. ¶ 6. The assay developed by Holodniy at Cetus is cited and described in the '730 patent. Rhyu Dec., Exh. 15 at col. 13:64–66; Holodniy Dec. ¶ 26. In 1995, Holodniy, Merigan and Katzenstein executed an assignment purporting to convey their interests in the '730 and '705 patents to Stanford. JSUF 92. Stanford recorded these assignments with the PTO on June 9, 1995. Id. Roche knew of the '730, '086, '128 and '268 patents as of December 1999. Rhyu Dec., Exh. 681 at Resp. to Interrog. No. 10. In 1998, Stanford attempted to license the '268 and '128 patents. In October 1998, Dr. Tom White, Senior Vice

President of Research and Development at Roche, received a copy of a letter that Stanford had sent to the Laboratory Corporation of America (LabCorp) seeking to license the patents to LabCorp. White Dep. at 209:13–210:20, 214:16–215:10; Rhyu Dec., Exh. 554; Mejia Dec. ¶ 9. White testified that he wrote a note on the letter listing the names of Roche personnel to whom he intended to send the letter, though he could not recall forwarding the letter to anyone at Roche. White Dep. at 214:16–215:25. In addition, on April 6, 2000 a Senior Licensing Associate at Stanford made a presentation to Roche's Director of Licensing attempting to license the technology to Roche. Mejia Dec. ¶ 10; Rhyu Dec., Exh. 693. The presentation included statements to the effect that the value of the quantification developed at Cetus was not evident to Cetus through June 1992, and referred to the '730 patent family as "Stanford IP." Rhyu Dec., Exh. 693 at STAN 029331, 029334, 029340. At this presentation, the Roche personnel did not assert rights in the patent family. Mejia Dec. ¶ 12.

In 1991, Hoffman-La Roche, Inc. acquired all of Cetus' PCR assets via an Assets Purchase Agreement. Chiang Dec., Exh. 44 at RMS 6318, 6333–34. The assets included personal property, certain specified PCR intellectual property, Cetus' rights under transferred contracts, and Cetus' rights under any confidentiality agreements. Id. at RMS 6333-34 § 2.1(a)–(g). Hoffman-La Roche also purchased license rights to any intellectual property used in the PCR business that was not listed as transferred intellectual property. Id. at RMS 6339 § 2.8(b). Schedules attached to the APA delineated the "Transferred Intellectual Property" and "Transferred Contracts" Id. at RMS 6444-6547. The transferred intellectual property

relevant to this motion includes: (1) the invention disclosure form submitted by Konrad on behalf of Holodniy, and (2) "All PCR Technology . . . that is contained in the following documents to the extent of [Cetus'] interest: . . . all files, book and records and laboratory notebooks of the PCR Business . . ." Id. at RMS 06460, 06464. The transferred contracts relevant to this motion include (1) Holodniy's February 14, 1989 Visitor's Confidentiality Agreement and (2) the 1988 MTA. Id. at RMS 06481, 06524. The cRNA standard and the plasmid strain that serves as the master copy for that standard were transferred specifically to Roche. Nersesian Dec. ¶¶ 3–10, Exhs. 1–5. The consulting agreements entered into by Merigan and Cetus in 1984 and 1991 are not listed in the APA.

LEGAL STANDARD

Summary judgment is proper when the pleadings, discovery, and affidavits show that there is "no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(c). Material facts are those which may affect the outcome of the proceedings. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248 (1986). A dispute as to a material fact is genuine if there is sufficient evidence for a reasonable jury to return a verdict for the nonmoving party. Id. The party moving for summary judgment bears the burden of identifying those portions of the pleadings, discovery, and affidavits that demonstrate the absence of a genuine issue of material fact. Celotex Corp. v. Catrett, 477 U.S. 317, 323 (1986). On an issue for which the opposing party will have the burden of proof at trial, the moving party need only point out "that there is an

absence of evidence to support the nonmoving party's case." Id.

Once the moving party meets its initial burden, the nonmoving party must go beyond the pleadings and, by its own affidavits or discovery, "set forth specific facts showing that there is a genuine issue for trial." Fed. R. Civ. P. 56(e). Mere allegations or denials do not defeat a moving party's allegations. Id.; see also Gasaway v. Northwestern Mut. Life Ins. Co., 26 F.3d 957, 960 (9th Cir. 1994). The court may not make credibility determinations, Anderson, 477 U.S. at 249, and inferences drawn from the facts must be viewed in the light most favorable to the party opposing the motion. Masson v. New Yorker Magazine, 501 U.S. 496, 520 (1991).

DISCUSSION

Roche asserts that it is entitled to summary judgment on its claims as to ownership and license on three grounds. First, Roche claims that it acquired, through Cetus, an ownership interest in the '730 and '705 patents as a result of the VCA signed by Holodniy. Second, Roche claims that the 1988 MTA between Stanford and Cetus grants Roche a royalty-free nonexclusive license to the '730 and '705 patents. Finally, Roche asserts that, because the PCR assay was developed in Cetus' laboratories, Roche acquired a "shop rights" license to the patents.[4]

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[4] Roche additionally makes the absurd claim that, as the plaintiff in this action, Stanford must show that it has title in the patents and therefore Stanford bears the burden of proving Roche's lack of ownership. This is fundamentally incorrect. Patent rights presumptively vest in the named inventors on the patent. Beech

Stanford claims that the 1988 MTA did not grant an ownership right, but granted only an option that was never exercised. Stanford further claims that the terms of the VCA preclude Roche from asserting any rights based on this contract. Stanford also disputes Roche's claim to "shop rights," because the invention disclosed in the '730 and '705 patents were not "conceived and perfected" at Cetus and equitable considerations do not warrant the imposition of shop rights. In addition to these substantive challenges, Stanford asserts that Roche's ownership and license claims are time-barred. Specifically, Stanford argues that Roche's claims are barred by the statute of limitations, by the doctrine of laches, and by equitable estoppel. Stanford additionally seeks summary judgment that Roche acquired no rights via the MTAs between Cetus and Merigan in 1984 and 1991.

I. Timeliness[5]

A. Statute of Limitations

Aircraft Corp. v. EDO Corp., 990 F.2d 1237, 1248 (Fed. Cir. 1993); Arachnid, Inc. v. Merit Indus., Inc., 939 F.2d 1574, 1578 n.2 (Fed. Cir. 1991). Title to the patent therefore presumptively rests with Stanford, the named assignee, and Roche is tasked with overcoming this presumption to defeat Stanford's standing.

[5] Stanford's timeliness arguments are principally directed towards the claims at issue here--ownership and license. In a footnote, Stanford suggests that, if the court dismisses these claims based on timeliness or estoppel, the court should also dismiss Roche's breach of contract and specific performance claims in the interests of judicial economy. Because these claims have not been fully briefed by either side, however, the court declines Stanford's suggestion and will not address claims other than ownership and license.

Roche asserts that it is an owner of the patents at issue, a licensee of the patents, and that Stanford lacks standing because it is not the exclusive owner of the patents. Stanford contends that these claims are governed by California's four-year statute of limitations for written contracts, or alternatively by California's residuary four-year statute of limitations for any actions not otherwise addressed by specific statute. CAL. CIV. PROC. CODE § 337(1), 343.

Roche responds that, notwithstanding the counterclaim appellation, its three claims against plaintiff are actually "defenses." Applying this characterization, defendant invokes the well-worn rule that "a statute of limitations should be used only as a shield, not a sword." City of St. Paul, Alaska v. Evans, 344 F.3d 1029, 1033 (9th Cir. 2003). In other words, claims that would otherwise be time-barred may nonetheless be raised as defenses. Id. Because Roche has pleaded its ownership and license claims both as counterclaims and affirmative defenses, resolution of this matter depends in part on whether these claims are better recognized as defenses or as counterclaims in general. See Fed. R. Civ. P. 8(c) (giving the court discretion "if justice so requires" to treat a mistakenly designated defense as a counterclaim and vice versa). Where, as here, jurisdiction is premised on a federal question, the federal rules control. Benny v. Pipes, 799 F.2d 489, 493 (9th Cir. 1986).

The affirmative defense is a descendant of the old plea of "confession and avoidance," whereby a defendant admits the plaintiff's prima facie case, and then alleges additional material that defeats the plaintiff's cause of action. 5 CHARLES ALAN WRIGHT & ARTHUR R. MILLER, FEDERAL PRACTICE AND

PROCEDURE § 1270, at 558 (3d ed. 2004). Federal Rule of Civil Procedure 8(c) spells out a list of those matters constituting affirmative defenses, and while the list is not exhaustive, it is instructive. Roche has counterclaimed that it has a license to the rights of the patents in issue, and a license is one of the matters listed in Rule 8(c) as an affirmative defense. Worldwide Church of God v. Philadelphia Church of God, Inc., 227 F.3d 1110, 1114 (9th Cir. 2000). However, Roche's two remaining contentions—that it is an owner of the patents, and the related claim that Stanford lacks standing because it is not the exclusive owner of the patents—are not among those listed. More importantly, those two claims are not in the nature of "confession and avoidance," but rather are direct refutations of plaintiff's prima facie case.

Time-barred claims may be raised as defenses in other limited situations, most commonly in the context of equitable recoupment, where a party may raise a time-barred claim for an offset as a defense to prevent unjust enrichment. See City of St. Paul, 344 F.3d at 1034. This is due in part to the fact that the defendant in that circumstance is not seeking "affirmative recovery on an identical claim." Id. at 1035. But where a defendant seeks more than adjudication of questions raised by way of defense, and instead seeks affirmative recovery via counterclaim, it "abandon[s] its right to seek solace in the status of a defendant." Id. at 1036. Roche's claim as licensee seeks no affirmative recovery, but only to preserve the status quo, and is better viewed as an affirmative defense. As such, it is entitled to the traditional shield from a statute of limitations-based attack. Roche's claims of ownership of the patents and that Stanford lacks standing as the non-exclusive owner of the patents seek to expand

Roche's current rights, and are properly viewed as counterclaims subject to the applicable statute of limitations.

The proper statute of limitations must then be applied to Roche's counterclaims. It is well-established that where federal jurisdiction is premised on diversity, the federal court must apply the applicable state statute of limitations. Nevada Power Co. v. Monsanto Co., 955 F.2d 1304, 1306 (9th Cir. 1992). While authority is less clear on the applicable statute of limitations for an ancillary state law claim where jurisdiction is premised on a federal question, the court has little hesitation in applying California's statute of limitations to claims based on contracts that are themselves governed by California law. No party has suggested that an alternative statute of limitations should be applied.

Generally the statute of limitations begins to run under California law at "the time when the cause of action is complete with all of its elements." Norgart v. Upjohn Co., 21 Cal. 4th 383, 397 (1999). However, the running of the statute may be postponed by the discovery rule, which postpones accrual of a cause of action until the claimant discovers the cause of action. Id. The claimant discovers his cause of action when he becomes aware of facts which would make a reasonably prudent person suspicious that he had been injured — in the contract context, that the contract had been breached in some manner. Miller v. Bechtel Corp., 33 Cal. 3d 868, 875 (1983). Because of this arousal of suspicion, the claimant is charged with knowledge of those facts which further investigation would have revealed. Id.

Stanford has put forth substantial evidence indicating that Roche knew or should have known that Stanford was acting as the sole owner of the patents no later than April 2000. Roche has not presented any evidence or argument to the contrary. Indeed, Roche admitted in discovery that it knew of the '730 patent as early as 1999. Rhyu Dec., Exh. 681 at Resp. to Interrog. No. 10. Rather, Roche rests its entire defense against the statute of limitations on its assertion that such claims cannot be raised against defenses or counterclaims, which is a misstatement of the law as it relates to its ownership claims. The court holds that Roche's ownership claims are barred as untimely. Roche may proceed with its license claims only.

Furthermore, because Roche's claim that Stanford lacks standing to bring suit is dependent upon Roche's showing that Roche is an owner of the patents-in-suit, Roche's inability to pursue its ownership claim is fatal to its argument regarding Stanford's standing.

B. Laches

"Laches is an equitable defense that prevents [a suit by] a plaintiff, who with full knowledge of the facts, acquiesces in a transaction and sleeps upon his rights." Danjaq LLC v. Sony Corp., 263 F.3d 942, 950–951 (9th Cir. 2001) (internal quotations omitted). "To demonstrate laches, the defendant must prove both an unreasonable delay by the plaintiff and prejudice to itself." Id. at 951. Stanford asserts that Roche failed to pursue its ownership claim despite its knowledge that Stanford was acting as the patents' sole owner. Stanford further asserts that Roche's delay has prejudiced Stanford in that (1) Stanford has expended substantial resources in licensing and

litigation activities related to the patents and (2) Roche's delay has created a loss of evidence and rendered pertinent recollections unreliable. Roche responds, via footnote, that Roche claimed ownership in the patents via pre-litigation discussions in February through April 2004 (Boozell Dec., Exhs. 2–5), and claims that Stanford's asserted prejudice regarding its licensing and litigation efforts relates only to patents which, while part of the '730 patent family, are not at issue in this motion. Roche raises no objection to Stanford's claim that it has been prejudiced by the loss of evidence. Such "evidentiary prejudice" is sufficient to warrant the imposition of laches when coupled with unreasonable delay. Id. at 955 (identifying "such things as lost, stale, or degraded evidence, or witnesses whose memories have faded or who have died" as one of "two chief forms of prejudice in the laches context").

As for the delay, Roche's argument misconstrues the nature of laches. The fact that Roche may have been behaving as an owner of the patent during the relevant time period does not toll the delay. Rather, "the relevant delay is the period from when the plaintiff knew (or should have known) of the allegedly infringing conduct, until the *initiation of the lawsuit* in which the defendant seeks to counterpose the laches defense." Id. at 952 (finding unreasonable delay on the part of counterclaimant where, until party filed its counterclaim, the party "took no *legal* action to stop, or to seek redress for, the alleged infringements") (all emphasis added). Nor is Roche's pre-litigation correspondence with Stanford asserting its rights relevant in determining the laches period. The relevant delay is the delay in "instituting litigation," not the delay in "bringing claims to the attention of the

defendant." Nealey v. Transportacion Maritima Mexicana, S.A., 662 F.2d 1275, 1280 (9th Cir. 1980) (internal quotations omitted). Roche offers no justification for its delay in bringing suit to resolve its ownership interest in the patents. Rather, Roche simply denies the existence of the delay.

Because Roche's delay in suing to enforce its ownership interest is unreasonable and has at least caused substantial evidentiary prejudice to Stanford, Roche's ownership claims are barred by the doctrine of laches.

C. Equitable Estoppel

Stanford further asserts that Roche should be barred from asserting defenses or counterclaims of ownership and license based on the doctrine of equitable estoppel. Unlike the statute of limitations, which is a technical legal requirement, equitable estoppel applies where equity and justice require that a party be prevented from asserting its legal rights against another. Granite State Ins. Co. v. Smart Modular Techs., Inc., 76 F.3d 1023, 1027 (9th Cir. 1996). Under California law,[6] the elements of equitable estoppel are:

> (1) the party to be estopped must be apprised of the facts; (2) [the party to be estopped] must intend that his conduct shall be relied upon, or must so act that the party asserting the estoppel had a right to believe it was so

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[6] The parties agree that California, rather than federal, law controls the question of equitable estoppel.

> intended; (3) the [party asserting estoppel] must be ignorant of the true state of facts; and (4) [the party asserting estoppel] must rely upon the conduct to his injury.

Id. at 1028, citing Driscoll v. City of Los Angeles, 67 Cal. 2d 297, 306 (1967). In matters involving title to property, "the culpability of the party to be estopped must be of sufficient dimension that actual or constructive fraud would result if the estoppel were not raised." City of Long Beach v. Mansell, 3 Cal. 3d 462, 491 (1970). It is once again necessary, therefore, to draw a distinction between Roche's license claims and Roche's ownership claims. Further, as Roche's ownership claims are barred as untimely, the court need only consider equitable estoppel as it may apply to Roche's license claims.

Stanford's factual argument in regard to the elements of equitable estoppel is limited to Roche's claims of ownership. Essentially, Stanford argues that Roche abandoned any ownership interest it ever had in the patents, and that Stanford relied on this abandonment in continuing its research, prosecuting and obtaining its patents, licensing the patents, and asserting its patent rights via litigation. Such assertions say nothing of Roche's purported status as a licensee, and Stanford makes no showing that Roche knew Stanford believed it was not a licensee, that Roche intended to induce reliance by acting as a licensee, that Stanford was unaware that Roche was practicing the invention during the relevant time period, or that Stanford relied to its detriment on Roche's allegedly secretive licensee conduct. Accordingly, Roche's license claims are not barred by equitable estoppel.

II. The Holodniy VCA

Roche asserts that the Holodniy VCA assigned Holodniy's ownership interest in the patent to Cetus, and therefore Roche acquired Holodniy's rights to the patent via the APA. Because Roche claims only an ownership right from the Holodniy VCA, this claim is barred as untimely as discussed above. However, because the effect of the Holodniy VCA has been raised and extensively argued by the parties, the court will address the issue.

The operative language in the VCA is:

> If, as a consequence of my access to CETUS' facilities or information, I conceive of or make, alone or with others, ideas, inventions and improvements thereof or know-how related thereto that relate in any manner to the actual or anticipated business of CETUS, I will assign and hereby do assign to CETUS, my right, title, and interest in each of the ideas, inventions and improvements thereof described in this paragraph.

Chiang Dec., Exh. 11 ¶ 3. Roche claims that the PCR assay falls under the VCA, that the VCA amounted to an assignment of Holodniy's rights in the PCR assay to Cetus, and that Roche acquired Cetus' rights via the APA. Stanford raises a number of defenses to the application of the VCA to the patents-in suit. First, Stanford claims that Holodniy used only non-confidential information in developing the PCR assay, and that interpreting the VCA to include public information would render the agreement unenforceable under California law. Second, Stanford

claims that Holodniy had no rights to assign because the project Holodniy was working on was funded by the federal government, and therefore under the Bayh-Dole Act title Stanford had a superior right to the invention. Third, Stanford asserts that a genuine issue of fact exists as to whether the patented inventions were a "consequence" of Holodniy's access to Cetus as required under the VCA. Finally, Stanford claims that, even if Holodniy assigned his rights to Cetus via the VCA, Stanford has superior title to the patent as a subsequent bona fide purchaser.

A. California Business & Professions Code § 16600

Stanford claims that the publication of the PCR assay in the UCLA abstract and the JID article rendered the assay public, and therefore Holodniy's use of this information in developing the patented invention cannot fall under the VCA without rendering the agreement invalid under California law. California Business & Professions Code § 16600 provides: "Except as provided in this chapter, every contract by which anyone is restrained from engaging in a lawful profession, trade, or business of any kind is to that extent void." Courts have interpreted this provision such that anti-competition agreements are enforceable only to the extent necessary to protect trade secrets and prevent unfair competition. Winston Research Corp. v. Minn. Mining & Mfg. Co., 350 F.2d 134, 144–146 (9th Cir. 1965); Armorlite Lens Co. v. Campbell, 340 F. Supp. 273, 275 (S.D. Cal. 1972); Thompson v. Impaxx, Inc., 113 Cal. App. 4th 1425, 1430 (2003).

The only case in which the Federal Circuit has applied Section 16600 in the patent context appears to

be Litton Sys., Inc. v. Honeywell, Inc., 87 F.3d 1559 (Fed. Cir. 1996), cert granted, vacated on other grounds, Honeywell, Inc. v. Litton Sys., Inc., 520 U.S. 1111 (1997). There, the dissent argued that a non-compete provision that precluded the former employee for "15 years from using any ion-beam sputtering process to produce optical films for any high power laser application" other than for the former employer was "unenforceable absent a showing that it is supported by patent rights or other proprietary interests." Id. at 1583 (Bryson, J., concurring in part and dissenting in part). The majority rejected this interpretation of Section 16600, and did not premise the enforceability of the non-compete provision on the existence of a patent. Id. at 1573 n.3. It does not appear, therefore, that a protectable property interest is necessary for the VCA to be enforced with respect to Holodniy's invention. In any case, the assignment clause at issue would only function as a non-compete provision if it required Holodniy to assign an invention conceived after he left Cetus. In other words, if the patented invention was conceived while Holodniy was still working at Cetus, the VCA is enforceable with respect to Holodniy's interest in that invention. The issue as to whether the invention was truly conceived prior to the additional experimentation by Holodniy, Merigan, Katzenstein and Israelski at Stanford is strongly disputed among the parties.

Conception is "the completion of the mental part of invention." Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1227–28 (Fed. Cir. 1994). "It is 'the formation in the mind of an inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice.'" Id. at 1228 (quoting Hybridtech Inc v. Monoclonal

Antibodies, Inc., 802 F.2d 1367, 1376 (Fed. Cir. 1986)). "An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue." Id.

While the record demonstrates that the patented invention was not *completed* until after Holodniy left Cetus, the invention was clearly *conceived* at the latest when Holodniy had developed the PCR assay. Holodniy came to Cetus with the goal of "develop[ing] an assay at Stanford that [they] could use to monitor treatment." Holodniy Dep. at 152:20–153:11. Holodniy therefore arrived at Cetus with the specific intent to develop a PCR assay that could be used to monitor HIV treatment, which is precisely the method claimed in the patents-in-suit. Holodniy developed the assay at Cetus, and the assay was complete by the time Holodniy left. The UCLA abstract, in which the assay was published, stated that the assay "may be a useful marker for disease progression or monitoring antiviral therapy." Chiang Dec., Exh. 20. The JID article also stated that "[q]uantitation of infectious HIV RNA in cell-free serum by PCR may be useful as a marker for disease progression or in monitoring anti-viral therapy," and that "[s]erum PCR may provide an additional marker of disease progression and drug efficacy that could improve our ability to monitor the course of HIV infection." Chiang Dec., Exh. 22 at RMS 01471. Following this latter statement, the article concludes that "[f]urther studies will be necessary to validate this approach." Id. at RMS 01471. The specific method of using the assay to monitor HIV treatment was therefore clear in the minds of Holodniy and the other Stanford scientists when the assay was completed at Cetus.

Stanford argues that the invention was not complete when Holodniy left Cetus, and that no invention was "conceived" until after Holodniy, Merigan and Israelski performed further experiments at Stanford. Clearly, the work performed at Stanford by Holodniy, Merigan and Israelski was not insubstantial. After the PCR assay had already been published in the UCLA abstract and the JID article, the additional work at Stanford gave rise to a separate article in the Journal of Clinical Investigation setting forth the Stanford team's findings with respect to the PCR assay. Portions of the article were reproduced directly in Stanford's patent application. Holodniy's letter to Stanford's patent counsel identifies his work at Cetus and his work at Stanford as two separate major contributions, and states that the letter was "crucial to the invention." However, while this evidence demonstrates that the invention may not have been reduced to practice until after the Stanford experiments, it does nothing to defeat Roche's claim that the invention was conceived before Holodniy left Cetus. This conception created an interest on the part of Holodniy in the patent applications. See Burroughs Wellcome, 40 F.3d at 1228. This was sufficient to trigger the assignment provision in the VCA.

The Burroughs Wellcome case is highly instructive. There, the patents-in-suit covered "methods for using [AZT] in the treatment of persons infected with [HIV]." Id. at 1225. The named inventors had "set out with the general goal of finding a method to treat AIDS," and developed the chemical compound AZT. Id. at 1230. The inventors sent the AZT compounds to the National Institutes of Health for testing, and NIH scientists showed that AZT had "significant activity" against the types of retroviruses that cause AIDS. Id. at 1225–26.

The court held that the invention—the method of using AZT to treat AIDS—was conceived when the inventors developed the compounds, not after the NIH experiments confirmed their effectiveness. Id. at 1230. The court found that, by the time the NIH scientists completed their tests, the inventors "had more than a general hope or expectation. They had thought of the particular antiviral agent with which they intended to address the problem . . ." Id. Similarly, the Stanford scientists here had settled upon a particular PCR assay to use in monitoring HIV treatment before Holodniy left Cetus. Although substantial work remained to "validate" the effectiveness of the assay for its intended use, the scientists "had more than a general hope or expectation." Accordingly, the patented invention was conceived when the PCR assay was completed.[7]

Because the invention was conceived during Holodniy's consultancy at Cetus, the court need not reach the issue of the enforceability of the VCA to inventions conceived after Holodniy left Cetus. For the purposes of the instant motion, it is sufficient to hold that the VCA is enforceable in connection with Holodniy's interest in the patented invention.

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[7] The court reaches this conclusion based on the evidence available in the record. However, as Roche points out, Stanford has withheld its asserted conception date in discovery based on privilege. If Stanford were to disclose this information it may assist the court in this inquiry.

B. The Bayh-Dole Act[8]

The VCA effectively assigned any rights that Holodniy had in the patented invention to Cetus. This does not end the inquiry, however, as Stanford claims that Holodniy had no interest to assign based on the Bayh-Dole Act, 35 U.S.C. sections 200 et seq. Under the Bayh-Dole Act, contracts between research entities and the United States government whereby the government provides funding for research must contain provisions allowing the government to take title in any patents that are issued as a result of the government-funded research.

The Federal Circuit recently explained the operation of the Bayh-Dole Act and its implementing regulations:

> [A] Bayh-Dole violation grants the government *discretionary* authority to take title. [Campbell Plastics Eng'g & Mfg., Inc. v. Brownlee, 389 F.3d 1243, 1250 (Fed. Cir. 2004)] (regulation "vests *discretion* in the government in determining whether to invoke forfeiture when an invention has not been correctly disclosed to it." (emphasis added)). When a violation occurs, the government can choose to take action; thus, title to the patent may be voidable. However, it is not void: title remains with the named

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[8] Roche has moved to strike Stanford's argument related to the Bayh-Dole Act on a number of grounds, none of which are persuasive. Given the fact that Roche's ownership claim is barred as untimely, the court's discussion of the effect of the Bayh-Dole Act assumes without deciding that Stanford's argument is properly raised.

> inventors or their assignees. Nothing in the statute, regulations, or our caselaw indicates that title is automatically forfeited. The government must take an affirmative action to establish its title and invoke forfeiture.

Central Admixture Pharmacy Servs., Inc. v. Advanced Cardiac Solutions, P.C., No. 2006-1307, 2007 WL 967936, at *4 (Fed. Cir. Apr. 3, 2007) (emphasis in original).[9] Accordingly, the Bayh-Dole Act does not alter the general rule that title to a patent vests in the inventor or the designated assignee.

This case is somewhat complicated by the fact that the interests of the assignee (Stanford) and the named inventor (Holodniy) are divergent. In essence, Roche is arguing that, notwithstanding any contractual or other obligations Holodniy may have had with respect to Stanford or the government, Holodniy's agreement with Cetus transferred his interest in the patent to Cetus. This claim implicates an additional provision of the Bayh-Dole Act, concerning the allocation of rights among contracting entities and individual inventors:

> If a contractor does not elect to retain title to a subject invention in cases subject to this section,

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[9] Central Admixture and Campbell Plastics discuss the consequences of a "violation" of the Bayh-Dole Act. In Campbell Plastics, 389 F.3d at 1250, the violation was failure to properly disclose the invention. The analysis in these cases presumably applies equally to situations where a government-funded researcher declines to retain title to the invention. 37 C.F.R. § 401.14(d)(1) (providing that the government may obtain title to the invention "[i]f the contractor fails to disclose or elect title to the subject invention").

> the Federal agency may consider and after consultation with the contractor grant requests for retention of rights by the inventor subject to the provisions of this Act and regulations promulgated hereunder.

35 U.S.C. § 202(d). When the individual inventor is not a contracting party, therefore, the Bayh-Dole Act provides that the individual inventor may obtain title only after the government and the contracting party have declined to do so. See TM Patents, L.P. v. Int'l Bus. Machs. Corp., 121 F. Supp. 2d 349, 369 (S.D.N.Y. 2000) (holding that an individual inventor who failed to "execute the necessary forms with the Navy" did not obtain title to a patent on a government-sponsored invention). Thus, although title still vests in the named inventor, the inventor remains under a legal obligation to assign his interest either to the government or the nonprofit contractor unless the inventor acts within the statutory framework to retain title. Significantly, the inventor in Central Admixture, 2007 WL 967936 at *2, did just that:

> During patent prosecution, Dr. Buckberg designated UC as his assignee. On February 12, 1987, UC communicated to NIH its intent to abandon its interest in the pending application. One month later, Dr. Buckberg wrote to NIH to request that it waive patent rights in the application so that he could pursue the application in his personal capacity. See 35 U.S.C. § 202(d) (allowing agencies to grant such requests).

Here, there is no indication that Holodniy ever complied with the requirements of 35 U.S.C. section

202(d). In fact, the record indicates that Stanford elected to retain title, and therefore Section 202(d) was never implicated. Stanford submitted invention disclosures to the NIH explicitly electing to retain title in the patents, and citing 37 C.F.R. section 401, which implements 35 U.S.C. sections 202 through 204. Rhyu Supp. Dec., Exh. 710; 37 C.F.R. § 401.1(b). Roche offers no valid objections and no contrary evidence. Accordingly, Holodniy's purported assignment to Cetus conflicted with the legal requirements of the Bayh-Dole Act, which mandated that Stanford be given a superior right to retain title to the patents. In other words, the government had a right of first refusal regarding the patents, and Stanford had what amounted to a "right of second refusal" in the event the government declined to exercise its right. Because Stanford exercised its right and obtained title in the patents, Holodniy had no interest to assign to Cetus. The assignment provision in the VCA is therefore void as it applies to the '730 and '705 patents.[10]

C. Stanford's Status as a Subsequent Bona Fide Purchaser

In a further attempt to defeat the VCA, Stanford asserts that, if Holodniy assigned his rights in the patent to Cetus, Stanford has superior title as a subsequent bona fide purchaser of Holodniy's rights.

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[10] Stanford additionally cites FilmTec Corp. v. Hydranautics, 982 F.2d 1546 (Fed. Cir. 1992) for the proposition that, under the Bayh-Dole Act, title to patents on government-funded inventions vests automatically in the United States government. That case, however, dealt with the Federal Nonnuclear Energy Research and Development Act, not the Bayh-Dole Act.

35 U.S.C. section 261 provides that, with respect to interests in patent applications,

> An assignment, grant or conveyance shall be void as against any subsequent purchaser or mortgagee for a valuable consideration, without notice, unless it is recorded in the Patent and Trademark Office within three months from its date or prior to the date of such subsequent purchase or mortgage.

Holodniy signed the VCA on February 14, 1989, and assigned his rights in Patent Application No. 07/883,327 to Stanford by an instrument dated May 4, 1995. Chiang Dec., Exh. 11; Rhyu Supp. Dec., Exh. 705 at PENNIE 000128–29. Stanford recorded the assignment with the PTO on June 9, 1995. Rhyu Supp. Dec., Exh. 706 at PENNIE 000315. The purported assignment from Holodniy to Cetus does not appear to have been recorded. Stanford also claims to have paid valuable consideration for Holodniy's assignment in the form of Holodniy's "employment and continued employment by Stanford," as reflected in the Copyright and Patent Agreement that Holodniy signed on June 28, 1988. Rhyu Supp. Dec., Exh. 23. Finally, Stanford asserts that it had no notice of Cetus or Roche's claims to the patent based on Holodniy's assignment.

Stanford's bona fide purchaser claim will fail if (1) Holodniy's knowledge of his assignment is imputed to Stanford or (2) Holodniy's "employment and continued employment by Stanford" is insufficient consideration to invoke the protections of Section 261.

In the context of determining whether a principal is a bona fide purchaser, "[t]he general rule is that a

principal is charged with the knowledge of the agent acquired by the agent in the course of the principal's business." Curtis, Collins & Holbrook Co. v. United States, 262 U.S. 215, 222 (1923). Holodniy was sent to Cetus by Merigan as part of Holodniy's employment as a research fellow at Stanford. Because Holodniy therefore signed the VCA in the course of Stanford's business, Holodniy's knowledge of the assignment is imputed to Stanford. Without delving further into the intricacies of an area of law that most lawyers are content to leave behind in law school, the court concludes that Stanford's imputed notice defeats its status as a subsequent bona fide purchaser of Holodniy's interest in the patents.

D. Construction of "as a consequence of"

Finally, Stanford disputes that the PCR assay and the patented invention were developed "as a consequence of" Holodniy's access to Cetus' facilities or information, as required for assignment under the VCA. This contention merits little discussion. Holodniy's own testimony establishes that he went to Cetus with the goal of "develop[ing] an assay at Stanford that we could use to monitor treatment," that he spent nine months working onsite at Cetus, using Cetus equipment and materials and obtaining advice from Cetus personnel, and that he developed the PCR assay "with assistance from Cetus scientists while [he] was at Cetus." Holodniy Dep. at 252:20–24. Stanford's insistence that Holodniy "could have" developed the PCR assay based on information publicly available at the time does not change the fact that Holodniy *did* develop the PCR assay with substantial assistance from Cetus. The record unambiguously reflects that the PCR assay and the ensuing patented invention

were developed "as a consequence of" Holodniy's access to Cetus' facilities and information.

III. The 1988 MTA

Roche claims that Cetus acquired a free, non-exclusive license to the '730 and '705 patents via the 1988 MTA executed by Merigan and Schwartz, which Roche then acquired through its acquisition of Cetus' PCR operations. In response, Stanford argues that (1) the MTA required subsequent actions on the part of Cetus to obtain any licenses, (2) Stanford would be entitled to royalties from a non-exclusive license, (3) no relevant materials were transferred under the MTA and therefore it never took effect, and (4) the MTA was not assignable and therefore no rights in the patents arising from the MTA could have been assigned to Roche.

A. Construction of the License Provision

Paragraph 8 of the MTA addresses inventions or substances "that may be commercially useful" resulting from the research involving the material subject to the agreement. The paragraph provides, in relevant part:

> In consideration of CETUS' providing of the Material, INSTITUTION, to the extent it is legally able to do so, hereby grants CETUS the first option to an exclusive license, at a reasonable royalty to be negotiated in good faith based on the respective parties' contributions and relevant industry standards, to use commercially the invention or substance, or at CETUS' option, a nonexclusive license.

Stanford asserts that this language granted Cetus two options for licenses. Stanford's interpretation is incorrect. The second use of the term "option" does not mean "option" in the contractual sense, but rather in the traditional sense of "choice." The MTA granted Cetus its choice between "the first option to an exclusive license, at a reasonable royalty" *or* "a nonexclusive license." The phrase "at CETUS' option" simply means that the decision as to whether Cetus obtained an option to an exclusive license or a nonexclusive license was Cetus' to make.

Citing extrinsic evidence, Stanford further asserts that it was entitled to royalties in the event that Cetus chose the nonexclusive license. This assertion, however, is contradicted by the plain language of the provision. There is nothing in the language of Paragraph 8 to indicate that the royalty clause applies to the nonexclusive license as well as the exclusive license. Stanford's argument that this interpretation renders the term "option" meaningless because a rational decisionmaker would always accept an option if it were free is unconvincing. The contract granted Cetus, by default, a free non-exclusive license. The contract further permitted Cetus to exercise an option to pay royalties for exclusivity. Either way, Cetus' right to use the inventions was secured by the MTA.[11]

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[11] Stanford's citation to the deposition testimony of its 30(b)(6) witness sheds no light on the interpretation of the MTA. The witness testified only to Stanford's general practice with respect to nonexclusive licenses, and specifically testified that he had no knowledge as to whether the license provision was subject to negotiation, whether it was drafted by Stanford or by Cetus, or the intent of the parties in drafting the provision. Stanford Dep.

Stanford further asserts that subsequent action was required on the part of Cetus to exercise its option to the nonexclusive license. The language of the contract is ambiguous on this point, and the factual record is unclear as to whether Cetus' conduct was consistent that of a nonexclusive licensee. The court need not resolve this ambiguity, however, in light of the holding below that any license rights obtained through the 1988 MTA could not have been assigned to Roche.

B. Transfer of Materials

In further defense against the 1988 MTA, Stanford claims that the licensing clause was never triggered because no materials were ever transferred within the meaning of the contract. Stanford asserts that the MTA covers only materials sent directly to Merigan or Schwartz, not to Holodniy or Stanford in general.

The portion of the MTA defining "Material" provides, in relevant part:

> The Material that is covered by this Agreement includes: (a) appropriate oligonucleotide primers and probes for the detection of human immunodefiency virus (HIV), HLA loci and both coded and noncoded control dilutions of HIV in uninfected DNA's to be used as controls for use with CETUS's proprietary polymerase chain reaction (PCR), and associated PCR technology; (b) any related biological material or associated

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at 281:11–282:11. There is nothing to indicate that Stanford did not deviate from its usual practice in signing the 1988 MTA.

> know-how and data that will be received by SCIENTIST from CETUS; and (c) any substance and associated know-how and data that are replicated ~~or derived therefrom~~ by SCIENTIST or his/her co-workers.

Chiang Dec., Exh. 10 ¶ 2 (strikeout in original). "SCIENTIST" is defined as Merigan and Schwartz. Id. at ¶ 1. In addition to Cetus, Merigan and Schwartz, Stanford was also a party to the MTA, identified in the contract as "INSTITUTION." Id. The language of the provision implies that the material includes: (1) primers, probes, loci and control dilutions originating with Cetus, regardless of who receives them; (2) related biological material or associated know-how and data received from Cetus by Merigan or Schwartz, and (3) substances and associated know-how and data replicated (but not derived) from the second category of materials by Merigan, Schwartz, or their co-workers at Stanford.[12] Because Stanford is a signatory to the contract, the provisions of the MTA regarding the use of the material by the "INSTITUTION" presumably apply to employees of

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[12] In a footnote, Stanford asserts that, because subparagraph 2(a) does not specify the parties involved in the transfer of materials, it should be interpreted in context to be limited to materials received from Cetus by Merigan and Schwartz. This interpretation would render the inclusion of the phrase "received by SCIENTIST from CETUS" in subparagraph 2(b) superfluous, and is therefore unsound in terms of contract interpretation. A more reasonable interpretation is that subparagraph 2(b) is limited to materials received by Merigan and Schwartz, subparagraph 2(c) is limited to materials replicated by Merigan, Schwartz or their co-workers, and subparagraph 2(a), lacking any party limitation, applies to any use or receipt of the delineated materials within the "INSTITUTION" (Stanford).

Stanford, including Holodniy. Given the specification of individual recipients or agents in the second two categories and the lack of such specification in the first category, the MTA was effective if Holodniy received and worked with any of the materials delineated in the first category.

Based on the parties' Joint Statement of Undisputed Facts, Holodniy received and used "avidin-coated beads and biotin labeled PCR primers," "SK-38 and SK-39 primers," "horseradish peroxide (HRP) labeled SK-19," and "advice and suggestions on a procedure to use HRP-labeled probes in the detection of PCR product." JSUF ¶¶ 14, 16, 17 & 29. Holodniy, as a Stanford researcher, used these primers and probes in developing the PCR assay that gave rise to the patented inventions. Accordingly, although Roche presents no evidence that materials were transferred directly to Merigan and Schwartz, Holodniy's receipt and use of the materials in connection with Stanford's development of the PCR assay method was sufficient to trigger the licensing provision and grant Cetus a nonexclusive license in the patented inventions.

In addition, Holodniy went to Cetus at Merigan's direction, as a researcher in Merigan's lab, shortly after the MTA was executed. This strongly suggests that Holodniy was dispatched as Merigan's agent in developing the PCR assay using Cetus' materials. Allowing Merigan to escape the license clause by acquiring the materials through Holodniy would defeat the purpose of the provision.

C. Assignment of the MTA Rights

Finally, Stanford argues that Cetus could not assign its rights under the MTA to Roche. Stanford bases this claim on two grounds. First, Stanford asserts that nonexclusive patent licenses can be assigned to a third party only with the consent of the licensor. Second, Stanford asserts that, under the terms of the MTA, the MTA is not assignable without the prior written consent of Cetus' Senior Vice President of Research and Development, and that no such written consent exists. In response, Roche argues that patent licenses are "freely transferable" where the license itself permits assignment. Roche further asserts that the written consent of Cetus' Vice President was not strictly required because it is either not a condition or it is a condition for Cetus' benefit subject to Cetus' waiver.

The assignability of patent licenses is governed by federal law, even where the contract at issue would generally be governed by state law. In re CFLC, Inc., 89 F.3d 673, 679 (9th Cir. 1996). A nonexclusive patent license "cannot be assigned unless the patent owner authorizes the assignment or the license itself permits assignment." Id. (quoting Gilson v. Republic of Ireland, 787 F.2d 655, 658 (D.C. Cir. 1986)). Since Stanford clearly has not consented to an assignment of any license whatsoever to Roche, Roche acquired the license granted in the MTA only if the MTA can be construed to allow the assignment. The assignability of the license must be expressly stated in the contract at issue. Stenograph Corp. v. Fulkerson, 972 F.2d 726, 729 n.2 (7th Cir. 1992); PPG Indus., Inc. v. Guardian Indus. Corp., 597 F.2d 1090, 1093 (6th Cir. 1979). Courts require compelling evidence of parties' intent

before a right to assign will be implied absent explicit language. Verson Corp. v. Verson Int'l Group PLC, 899 F. Supp. 358, 363 (N.D. Ill. 1995).

The only provision governing assignment is Paragraph 12, which states: "This Agreement is not assignable, whether by operation of law or otherwise, without the prior written consent of the Senior Vice President of Research and Development at CETUS." Chiang Dec., Exh. 10 ¶ 12. Roche and Stanford disagree as to the role of the written consent under this provision. Stanford interprets written consent as a prerequisite that must be fulfilled in addition to Stanford's consent in order to assign the license. Roche interprets this provision as affirmatively permitting assignment so long as Cetus consents.[13] The rule requiring express assignability combined with the policy considerations underlying the default unassignability of nonexclusive patent licensees counsels in favor of Stanford's position. The purpose of the non-assignability rule is to protect the patent holder's interest in controlling the identity of its licensees. In re CFLC, 89 F.3d at 679. The licensor's consent to assignment, whether in the form of express consent to a particular assignment or explicit language in the licensing instrument, is thus the hallmark of assignability. See id. at 680 (phrasing the rule such that nonexclusive licenses are "assignable only with

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[13] Roche acknowledges that the specific formality required by the assignment clause—written consent by the Senior Vice President of Research and Development—has not been fulfilled. Roche argues that this is unnecessary because it is not a condition, or if it is a condition it can be waived by Cetus as the benefactor of the condition. Because it is Stanford's consent that controls the situation, the court declines to reach this issue.

the consent of the licensor"). Nothing in the MTA language indicates Stanford's unambiguous intent to allow Cetus to assign the nonexclusive license obtained via Paragraph 8. Accordingly, Cetus could not have assigned its license in the patented inventions to Roche.[14]

IV. Shop Rights

Roche asserts that, in addition to any interests in the patented invention that Cetus may have obtained via contract, Cetus obtained a free, nonexclusive license to practice the inventions via "shop rights" because Holodniy developed the PCR assay at Cetus. Roche further asserts that these shop rights were part of the PCR intellectual property that was transferred to Roche via the APA.

As the Ninth Circuit has observed:

> The doctrine of shop rights has its origins in equity. A shop right is an employer's nonexclusive right to use an employee's patented process or invention that was developed during the employee's hours of

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[14] Roche additionally asserts that nonexclusive, contractual licenses are freely transferrable where the license is transferred in connection with the sale of a business. The Ninth Circuit did not articulate the sale of a business as an exception to the rule requiring the licensor's consent. Accordingly, the "sale of business" exception appears to be limited to equitable "shop right" licenses rather than contractual licenses. See California Eastern Labs., Inc. v. Gould, 896 F.2d 400, 402 (9th Cir. 1990). This doctrine is discussed in connection with Roche's shop rights claim in the following section.

> employment. The right is based on the employer's presumed contribution to the invention through materials, time, and equipment.

California Eastern Labs., 896 F.2d at 402. As the Supreme Court has explained, shop rights attach where the employment relationship does not involve any specific contractual provisions calling for the assignment of intellectual property. See United States v. Dubilier Condenser Corp., 289 U.S. 178, 187–88 (1933). Conversely, where an employment relationship specifically anticipates the development and assignment of intellectual property and sets conditions for assignment, the equitable remedy of shop rights is inapplicable. Here, Holodniy's relationship with Cetus was governed by a contract containing an explicit assignment provision, the conditions of which do not appear to have been met. Having failed to satisfy the contractual mechanism of obtaining rights in Holodniy's invention, Cetus cannot invoke shop rights as a back-up plan. Accordingly, Cetus does not own any shop rights in Holodniy's inventions.

V. The Merigan Consulting Agreements

Although Roche has not moved for summary judgment based on the Merigan Consulting agreements, Stanford seeks summary judgment that Roche has no ownership or license rights arising from those agreements. To the extent that the Merigan Agreements purport to grant ownership to Cetus, any claims Roche raises in these regards are either barred by the statute of limitations or defeated by the Bayh-Dole Act. Furthermore, if the Merigan Agreements granted nonexclusive licenses to Cetus in

the patented invention, these contractual rights are non-transferable absent the assent of Stanford. Roche points to nothing in the agreements that would absolve them of these defects. Accordingly, the court declines to address the unique arguments raised by Stanford with respect to the Merigan agreements.

CONCLUSION

For the foregoing reasons, Roche's motion for summary judgment is DENIED, and Stanford's motion for summary judgment is GRANTED in part and DENIED in part.

IT IS SO ORDERED.

Dated: April 16, 2007

/s/ Marilyn H Patel
MARILYN HALL PATEL
District Judge
United States District Court
Northern District of California

APPENDIX C

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2008-1509, -1510

[Filed December 22, 2009]

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiff/Counterclaim Defendant-Appellant,

and

THOMAS MERIGAN and MARK HOLODNIY,

Counterclaim Defendants,

v.

ROCHE MOLECULAR SYSTEMS, INC., ROCHE DIAGNOSTICS CORPORATION, ROCHE DIAGNOSTICS OPERATIONS, INC.,

Defendants/Counterclaimants-Cross Appellants.

Appeals from the United States District Court for the Northern District of California in case no. 05-CV-04158, Judge Marilyn Hall Patel.

ORDER

NOTE: This order is nonprecedential.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ORDER

A combined petition for panel rehearing and for rehearing en banc having been filed by the Appellant, and a response thereto having been invited by the court and filed by the Cross-Appellants,* and the petition for rehearing and response, having been referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and response having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for panel rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for rehearing en banc be, and the same hereby is, DENIED.

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* Amici curiae Wisconsin Alumni Research Foundation, et al. were granted leave to file a brief in support of Appellant's combined petition for rehearing.

The mandate of the court will issue on December 29, 2009.

FOR THE COURT,

/s/ Jan Horbaly
Jan Horbaly
Clerk

Dated: 12/22/2009

cc: Ricardo Rodriguez
Adrian M. Pruetz
Michelle M. Umberger

BD TRUSTEE LELAND V ROCHE MOLECULAR,
2008-1509 - 1510
(DCT - 05-CV-04158)

APPENDIX D

United States Court of Appeals for the Federal Circuit

2008-1509, -1510

[Filed December 29, 2009]

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiff/Counterclaim Defendant-Appellant,

and

THOMAS MERIGAN and MARK HOLODNIY,

Counterclaim Defendants,

v.

ROCHE MOLECULAR SYSTEMS, INC., ROCHE DIAGNOSTICS CORPORATION, ROCHE DIAGNOSTICS OPERATIONS, INC.,

Defendants/Counterclaimants-Cross Appellants.

Judgment

ON APPEAL from the United States District Court for the Northern District of California

in CASE NO(S). 05-CV-04158

This CAUSE having been heard and considered, it is

ORDERED and ADJUDGED:

AFFIRMED-IN-PART, VACATED-IN-PART, and REMANDED

ENTERED BY ORDER OF THE COURT

DATED SEP 30 2009 /s/ Jan Horbaly/s.w.
Jan Horbaly, Clerk

ISSUED AS A MANDATE: DEC 29 2009

APPENDIX E

United States Code
Title 35. Patents
Part II. Patentability of Inventions
and Grant of Patents
Chapter 18. Patent Rights in Inventions
Made with Federal Assistance

35 U.S.C. § 200. Policy and objective

It is the policy and objective of the Congress to use the patent system to promote the utilization of inventions arising from federally supported research or development; to encourage maximum participation of small business firms in federally supported research and development efforts; to promote collaboration between commercial concerns and nonprofit organizations, including universities; to ensure that inventions made by nonprofit organizations and small business firms are used in a manner to promote free competition and enterprise without unduly encumbering future research and discovery; to promote the commercialization and public availability of inventions made in the United States by United States industry and labor; to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions; and to minimize the costs of administering policies in this area.

APPENDIX F

United States Code
Title 35. Patents
Part II. Patentability of Inventions
and Grant of Patents
Chapter 18. Patent Rights in Inventions
Made with Federal Assistance

35 U.S.C. § 201. Definitions

As used in this chapter--

(a) The term "Federal agency" means any executive agency as defined in section 105 of title 5, and the military departments as defined by section 102 of title 5.

(b) The term "funding agreement" means any contract, grant, or cooperative agreement entered into between any Federal agency, other than the Tennessee Valley Authority, and any contractor for the performance of experimental, developmental, or research work funded in whole or in part by the Federal Government. Such term includes any assignment, substitution of parties, or subcontract of any type entered into for the performance of experimental, developmental, or research work under a funding agreement as herein defined.

(c) The term "contractor" means any person, small business firm, or nonprofit organization that is a party to a funding agreement.

(d) The term "invention" means any invention or discovery which is or may be patentable or otherwise protectable under this title or any novel variety of plant which is or may be protectable under the Plant Variety Protection Act (7 U.S.C. 2321 et seq.).

(e) The term "subject invention" means any invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement: *Provided*, That in the case of a variety of plant, the date of determination (as defined in section 41(d) of the Plant Variety Protection Act (7 U.S.C. 2401(d))) must also occur during the period of contract performance.

(f) The term "practical application" means to manufacture in the case of a composition or product, to practice in the case of a process or method, or to operate in the case of a machine or system; and, in each case, under such conditions as to establish that the invention is being utilized and that its benefits are to the extent permitted by law or Government regulations available to the public on reasonable terms.

(g) The term "made" when used in relation to any invention means the conception or first actual reduction to practice of such invention.

(h) The term "small business firm" means a small business concern as defined at section 2 of Public Law 85-536 (15 U.S.C. 632) and implementing regulations of the Administrator of the Small Business Administration.

(i) The term "nonprofit organization" means universities and other institutions of higher education or an organization of the type described in section 501(c)(3) of the Internal Revenue Code of 1986 (26 U.S.C. 501(c)) and exempt from taxation under section 501(a) of the Internal Revenue Code (26 U.S.C. 501(a)) or any nonprofit scientific or educational organization qualified under a State nonprofit organization statute.

APPENDIX G

United States Code
Title 35. Patents
Part II. Patentability of Inventions
and Grant of Patents
Chapter 18. Patent Rights in Inventions
Made with Federal Assistance

35 U.S.C. § 202. Disposition of rights

(a) Each nonprofit organization or small business firm may, within a reasonable time after disclosure as required by paragraph (c)(1) of this section, elect to retain title to any subject invention: *Provided, however,* That a funding agreement may provide otherwise (i) when the contractor is not located in the United States or does not have a place of business located in the United States or is subject to the control of a foreign government, (ii) in exceptional circumstances when it is determined by the agency that restriction or elimination of the right to retain title to any subject invention will better promote the policy and objectives of this chapter (iii) when it is determined by a Government authority which is authorized by statute or Executive order to conduct foreign intelligence or counter-intelligence activities that the restriction or elimination of the right to retain title to any subject invention is necessary to protect the security of such activities or, (iv) when the funding agreement includes the operation of a Government-owned, contractor-operated facility of the Department of Energy primarily dedicated to that

Department's naval nuclear propulsion or weapons related programs and all funding agreement limitations under this subparagraph on the contractor's right to elect title to a subject invention are limited to inventions occurring under the above two programs of the Department of Energy. The rights of the nonprofit organization or small business firm shall be subject to the provisions of paragraph (c) of this section and the other provisions of this chapter.

(b)(1) The rights of the Government under subsection (a) shall not be exercised by a Federal agency unless it first determines that at least one of the conditions identified in clauses (i) through (iv) of subsection (a) exists. Except in the case of subsection (a)(iii), the agency shall file with the Secretary of Commerce, within thirty days after the award of the applicable funding agreement, a copy of such determination. In the case of a determination under subsection (a)(ii), the statement shall include an analysis justifying the determination. In the case of determinations applicable to funding agreements with small business firms, copies shall also be sent to the Chief Counsel for Advocacy of the Small Business Administration. If the Secretary of Commerce believes that any individual determination or pattern of determinations is contrary to the policies and objectives of this chapter or otherwise not in conformance with this chapter, the Secretary shall so advise the head of the agency concerned and the Administrator of the Office of Federal Procurement Policy, and recommend corrective actions.

(2) Whenever the Administrator of the Office of Federal Procurement Policy has determined that one or more Federal agencies are utilizing the authority of

clause (i) or (ii) of subsection (a) of this section in a manner that is contrary to the policies and objectives of this chapter, the Administrator is authorized to issue regulations describing classes of situations in which agencies may not exercise the authorities of those clauses.

(3) If the contractor believes that a determination is contrary to the policies and objectives of this chapter or constitutes an abuse of discretion by the agency, the determination shall be subject to the [FN1]section 203(b).

[(4) Redesignated (3)]

(c) Each funding agreement with a small business firm or nonprofit organization shall contain appropriate provisions to effectuate the following:

(1) That the contractor disclose each subject invention to the Federal agency within a reasonable time after it becomes known to contractor personnel responsible for the administration of patent matters, and that the Federal Government may receive title to any subject invention not disclosed to it within such time.

(2) That the contractor make a written election within two years after disclosure to the Federal agency (or such additional time as may be approved by the Federal agency) whether the contractor will retain title to a subject invention: *Provided,* That in any case where publication, on sale, or public use, has initiated the one year statutory period in which valid patent protection can still be obtained in the

United States, the period for election may be shortened by the Federal agency to a date that is not more than sixty days prior to the end of the statutory period: *And provided further,* That the Federal Government may receive title to any subject invention in which the contractor does not elect to retain rights or fails to elect rights within such times.

(3) That a contractor electing rights in a subject invention agrees to file a patent application prior to any statutory bar date that may occur under this title due to publication, on sale, or public use, and shall thereafter file corresponding patent applications in other countries in which it wishes to retain title within reasonable times, and that the Federal Government may receive title to any subject inventions in the United States or other countries in which the contractor has not filed patent applications on the subject invention within such times.

(4) With respect to any invention in which the contractor elects rights, the Federal agency shall have a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world: *Provided,* That the funding agreement may provide for such additional rights, including the right to assign or have assigned foreign patent rights in the subject invention, as are determined by the agency as necessary for meeting the obligations of the United States under any treaty, international agreement, arrangement of cooperation, memorandum of understanding, or similar arrangement, including

military agreement relating to weapons development and production.

(5) The right of the Federal agency to require periodic reporting on the utilization or efforts at obtaining utilization that are being made by the contractor or his licensees or assignees: *Provided,* That any such information as well as any information on utilization or efforts at obtaining utilization obtained as part of a proceeding under section 203 of this chapter shall be treated by the Federal agency as commercial and financial information obtained from a person and privileged and confidential and not subject to disclosure under section 552 of title 5.

(6) An obligation on the part of the contractor, in the event a United States patent application is filed by or on its behalf or by any assignee of the contractor, to include within the specification of such application and any patent issuing thereon, a statement specifying that the invention was made with Government support and that the Government has certain rights in the invention.

(7) In the case of a nonprofit organization, (A) a prohibition upon the assignment of rights to a subject invention in the United States without the approval of the Federal agency, except where such assignment is made to an organization which has as one of its primary functions the management of inventions (provided that such assignee shall be subject to the same provisions as the contractor); (B) a requirement that the contractor share royalties with the inventor; (C) except with respect to a funding agreement for the operation of a

Government-owned-contractor-operated facility, a requirement that the balance of any royalties or income earned by the contractor with respect to subject inventions, after payment of expenses (including payments to inventors) incidental to the administration of subject inventions, be utilized for the support of scientific research or education; (D) a requirement that, except where it proves infeasible after a reasonable inquiry, in the licensing of subject inventions shall be given to small business firms; and (E) with respect to a funding agreement for the operation of a Government-owned-contractor-operated facility, requirements (i) that after payment of patenting costs, licensing costs, payments to inventors, and other expenses incidental to the administration of subject inventions, 100 percent of the balance of any royalties or income earned and retained by the contractor during any fiscal year up to an amount equal to 5 percent of the annual budget of the facility, shall be used by the contractor for scientific research, development, and education consistent with the research and development mission and objectives of the facility, including activities that increase the licensing potential of other inventions of the facility; provided that if said balance exceeds 5 percent of the annual budget of the facility, that 75 percent of such excess shall be paid to the Treasury of the United States and the remaining 25 percent shall be used for the same purposes as described above in this clause (D); and (ii) that, to the extent it provides the most effective technology transfer, the licensing of subject inventions shall be administered by contractor employees on location at the facility.

(8) The requirements of sections 203 and 204 of this chapter.

(d) If a contractor does not elect to retain title to a subject invention in cases subject to this section, the Federal agency may consider and after consultation with the contractor grant requests for retention of rights by the inventor subject to the provisions of this Act and regulations promulgated hereunder.

(e) In any case when a Federal employee is a coinventor of any invention made with a nonprofit organization, a small business firm, or a non-Federal inventor, the Federal agency employing such coinventor may, for the purpose of consolidating rights in the invention and if it finds that it would expedite the development of the invention--

(1) license or assign whatever rights it may acquire in the subject invention to the nonprofit organization, small business firm, or non-Federal inventor in accordance with the provisions of this chapter; or

(2) acquire any rights in the subject invention from the nonprofit organization, small business firm, or non-Federal inventor, but only to the extent the party from whom the rights are acquired voluntarily enters into the transaction and no other transaction under this chapter is conditioned on such acquisition.

(f) (1) No funding agreement with a small business firm or nonprofit organization shall contain a provision allowing a Federal agency to require the licensing to third parties of inventions owned by

the contractor that are not subject inventions unless such provision has been approved by the head of the agency and a written justification has been signed by the head of the agency. Any such provision shall clearly state whether the licensing may be required in connection with the practice of a subject invention, a specifically identified work object, or both. The head of the agency may not delegate the authority to approve provisions or sign justifications required by this paragraph.

(2) A Federal agency shall not require the licensing of third parties under any such provision unless the head of the agency determines that the use of the invention by others is necessary for the practice of a subject invention or for the use of a work object of the funding agreement and that such action is necessary to achieve the practical application of the subject invention or work object. Any such determination shall be on the record after an opportunity for an agency hearing. Any action commenced for judicial review of such determination shall be brought within sixty days after notification of such determination.

APPENDIX H

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

Case No. C 05 04158 MHP

[Filed October 27, 2006]

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,	)
Plaintiff,	)
v.	)
ROCHE MOLECULAR SYSTEMS, ET AL.,	)
Defendants.	)
ROCHE MOLECULAR SYSTEMS, ET AL.,	)
Counterclaimants,	)
v.	)
THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY; THOMAS MERIGAN AND MARK HOLODNIY	)

Counterclaim Defendants.)
)

DECLARATION OF MARK HOLODNIY, M.D., IN SUPPORT OF COUNTERCLAIM DEFENDANTS STANFORD UNIVERSITY, DR. MERIGAN AND DR. HOLODNIY'S MOTION FOR SUMMARY JUDGMENT

I, MARK HOLODNIY, declare:

1. I am a Professor of Medicine at Stanford University. I have an M.D. from Northwestern University, and I completed a fellowship program in infectious diseases at the Stanford University School of Medicine.

2. I am also a named Counterclaim Defendant in this case. I submit this declaration in support of Stanford and Counterdefendants' Motion for Summary Judgment. I have knowledge of the following, and if called as a witness, I could and would testify competently to this declaration's contents.

3. I refer in this declaration to exhibits that are attached to Declaration of Michelle S. Rhyu, to be submitted concurrent with this declaration.

4. I am a named inventor on two U.S. patents: U.S. Patents Nos. 5,968,730 (the "'730 patent") and 6,503,705 (the "705 patent"). Both patents (collectively, "the monitoring patents") are entitled "Polymerase Chain Reaction Assays for Monitoring Antiviral Therapy and Making Therapeutic Decisions in the Treatment of Acquired Immunodeficiency Syndrome." These patents generally claim methods for evaluating

the effectiveness of anti-HIV therapy to make therapeutic decisions for treating patients with Acquired Immunodeficiency Syndrome (AIDS).

5. I joined Stanford as a post-doctoral fellow in the July of 1988. I spent the first few months in clinical rotations and began focusing on possible research projects in the fall of 1988. In the fall of 1988, I joined the lab of Dr. Thomas Merigan to begin a research project.

6. At the time I started working at Stanford, I signed a Copyright and Patent Agreement, A copy of that agreement is attached to the Rhyu Declaration as Exhibit 23

7. In or around the fall of 1988, Dr. Merigan and I discussed the shortcomings of existing assays for detecting and quantifying the level of HIV DNA in patient samples. We determined that I should direct my research to developing a better quantitative PCR-based assay for HIV than the one that existed at that time. To familiarize myself with the existing methods, I read the available literature relating to PCR assays.

8. My laboratory notebook from the period when I first joined the Merigan lab shows that I had been referring to specific publications and had performed PCR assays on HIV and HLA sequences, using primers that I had ordered from a company, Operon Technologies, in the fall of 1988. A copy of excerpts from lab notebook is attached to the Rhyu Declaration as Exhibits 5 and 7.

9. Many of the PCR-related publications as of 1988 had been published by scientists at Cetus Corp. in Emeryville. At that time Cetus was using a semi-quantitative assay. At some point in 1988 or 1989, Dr. Merigan and I decided that it would be helpful to work with Cetus scientists to develop an HIV assay that was capable of accurately measuring HIV copy number.

10. I understand that Roche claims that I received materials and information from Cetus under a "Materials Transfer Agreement" that was signed by Drs. Merigan and Schwartz. (See Exhibit 29.) I never knew that this agreement existed prior to this case. No one from Cetus or anywhere else ever told me that this Agreement existed, and no one ever indicated to me that they were giving me materials or information under this agreement. I never signed a Materials Transfer Agreement with Cetus.

11. In February of 1989, I started as a visiting scientist at Cetus. Sometime in that timeframe, I signed a Visitor's Confidentiality Agreement that was provided to me. I understood that the agreement concerned my obligations to Cetus' confidential information. I never understood that agreement to cover work that I did when I was not at Cetus and not using confidential information.

12. Starting around February 1989, I spent several days a week at Cetus testing different approaches to quantitation of HIV nucleic acid. I spoke to Alice Wang and Ernie Kawasaki about their work in quantitative PCR and to Shirley Kwok and John Sninsky about their work related to detection of HIV using PCR. I also had some interaction with other

Cetus employees, including Michael Konrad, Eric Groves, Sharon DeGroat, Sanne DeWitt, Clayton Casipit, and Sue Kim. When I visited, I worked in the laboratory of Eric Groves and Mike Konrad. None of these people ever told me that our conversations were confidential or that Cetus considered any of our conversations to be about trade secrets.

13. During the time that I visited Cetus, I worked on developing the HIV assay with scientists at Stanford. Although I obtained advice about PCR from Cetus scientists, my understanding is that no one at Cetus was assigned to work on the project with me. Certainly, no one at Cetus directed the work I performed, and Cetus never paid me any wage or salary.

14. During the time I visited Cetus, no one ever told me that any particular information I learned or any reagent I used was confidential. None of the materials given to me were ever labeled confidential. At any given time during this period, I kept a single notebook, which I carried back and forth between Cetus and Stanford. No one requested that I keep a separate notebook for work performed at Cetus, and no one asked me to leave my lab notebook at Cetus, either when I worked at Stanford, or after I stopped being a visiting scientist.

15. I returned to spending full time at Stanford in fall of 1989, after the Loma Prieta earthquake.

16. By fall of 1989, I had developed a working assay that allowed quantitation of HIV RNA copy number from patient serum samples. I continued to refine this assay in the Stanford laboratories with the

assistance of Sohini Sengupta, a Stanford lab technician, as well as Drs. Merigan and David Katzenstein.

17. It was and is my belief that the materials and basic protocols shared by Cetus in support of our joint work were not trade secrets or confidential information. The techniques, protocols, and information I learned during my time at Cetus were published prior to my arrival at Cetus, or shortly thereafter, as listed below:

(a) The reverse transcription PCR protocol used by Cetus scientists and disclosed to me at Cetus was published in 1989 in Kawasaki E., *Amplification of RNA,* in: Innis et al., *PCR Protocols: a Guide to Methods and Applications,* Berkeley, CA: Academic Press, 337-47 (1990). The JID article cites this as a prior publication at footnote 8. The Kawasaki article indicates that the first reported use of reverse transcription PCR to amplify RNA had been published in 1987 by Veres et al. in *The Molecular Basis of the Sparse Fur Mouse Mutation*, Science 237:415-17 (1987). Although the citation lists the date of publication as 1990, I understand that the actual date of publication was December 28, 1989. A copy of that publication is attached to the Rhyu Declaration as Exhibit 640.

(b) The sequences of all four DNA primers used to perform PCR in the JID article, SK 19, SK 38, SK 39, and SK 145, were published in Kellogg D.B., Kwok S., *Detection of Human Immunodeficiency Virus,* in: Innis et al., *PCR Protocols: a Guide to Methods and Applications,* Berkeley, CA: Academic Press, 337-47 (1990). The JID article cites this as a prior publication

at footnote 9. Although the citation lists the date of publication as 1990, I understand that the actual date of publication was December 28, 1989. A copy of that publication is attached to the Rhyu Declaration as Exhibit 694.

(c) The sequence of SK 19 primer was also published in 1987 in *Identification of Human Immunodeficiency Virus Sequences by Using In Vitro Enzymatic Amplification and Oligomer Cleavage Detection,* J. Virology, 61(5): 1690-94 (1987). A copy of that publication is attached to the Rhyu Declaration as Exhibit 536.

(d) The sequences of both the SK 38 and SK 39 primers were also published by Shirley Kwok and other Cetus scientists in 1988 in Ou et al., *DNA Amplification for Direct Detection of HIV-1 in DNA of Peripheral Blood Mononuclear Cells,* Science, 239:295-297 (1988). A copy of that publication is attached to the Rhyu Declaration as Exhibit 537.

(e) The sequence of the SK 145 primer was also published by Cetus in February 1990 in Kwok et al., *Effects of Primer-Template Mismatches on the Polymerase Chain Reaction: Human Immunodeficiency Virus Type 1 Model Studies,* Nucleic Acids Res., 18(4): 999-1005 (1990). A copy of that agreement is attached to the Rhyu Declaration as Exhibit 695.

(f) Cetus' protocols for biotinylation of SK 38 and horseradish peroxidase (HRP) labeling of SK 19 were published by Cetus in Levenson C., Chang, C., *Nonisotopically Labeled Probes and Primers,* in: Innis et al., *PCR Protocols: a Guide to Methods and Applications,* Berkeley, CA: Academic Press, 1990:337-

47 (1990). The JID article cites this as a prior publication at footnote 10. Although the citation lists the date of publication as 1990, I understand that the actual date of publication was December 28, 1989. This publication, which is a review article, establishes that the basic methods for labeling PCR primers with biotin and HRP had been described in scientific literature as early as 1985 and 1988, respectively, A copy of that publication is attached to the Rhyu Declaration as Exhibit 696.

(g) Isotopically labeled SK 19 was disclosed in 1987 in Kwok et al., *Identification of human Immunodeficiency Virus Sequences by Using In Vitro Enzymatic Amplification and Oligomer Cleavage Detection*, J. Virology, 61(5): 1690-94 (1987). A copy of that publication is attached to the Rhyu Declaration as Exhibit 536.

(h) The method of quantitative RT-PCR developed by Alice Wang was disclosed by Cetus in 1989 in Wang et al., *Quantitation of mRNA by the Polymerase Chain Reaction,* Proc. Natl. Acad. Sci., 86:9717-21 (1989). This publication disclosed the construction and use of an internal standard similar to the CC1 and CC2 RNA standards. A copy of that publication is attached to the Rhyu Declaration as Exhibit 12.

(i) The method of quantitative RT-PCR developed by Alice Wang was also disclosed by Cetus in Wang A., Mark D, *Quantitative PCR,* in: Innis et al., *PCR Protocols: a Guide to Methods and Applications,* Berkeley, CA: Academic Press, 1990:70-75 (1990). Although the citation lists the date of publication as 1990, I understand that the actual date of publication

was December 28, 1989. This publication also disclosed the construction and use of an internal standard similar to the CC1 and CC2 RNA standards. A copy of that publication is attached to the Rhyu Declaration as Exhibit 697.

18. With assistance from both Stanford and Cetus scientists, I ultimately developed an improved PCR assay for quantitating HIV RNA. One important difference between this assay and preexisting assays developed by Cetus is that this assay focused on HIV RNA sequences in patient serum, whereas prior Cetus assays had looked at detection of HIV in peripheral blood mononuclear cells. The decision to redirect the focus of my research to RNA quantitation in serum rather than DNA quantitation in cells was made without any input from Cetus scientists.

19. In or around December 1989, I prepared an abstract describing this research on a quantitative PCR assay for the UCLA Keystone Symposium on Molecular and Cellular Biology. This abstract was published, after obtaining Cetus' consent, under the title *Quantitation of HIV-1 RNA in Serum and Correlation with Disease Status Using Polymerase Chain Reaction,* in the Journal of Cellular Biochemistry, 14D (1990). The article lists Cetus scientists Alice Wang, Clayton Casipit, Mike Konrad, and Eric Groves as co-authors. I presented the abstract at the Keystone Symposium in March or April of 1990. A copy of that abstract is attached to the Rhyu Declaration as Exhibit 698.

20. Around the same time, I submitted an invention disclosure form to Cetus describing the assay for quantitating HIV RNA in serum that I had worked

on at Cetus. A copy of this invention disclosure form is attached to the Rhyu Declaration as Exhibit 34. Other than the request to fill out this disclosure form, Cetus never communicated to me any interest in patenting the described invention. I concluded that Cetus was not interested in pursuing further development of the RNA quantitative assay.

21. In early 1990, with Cetus' consent, Dr. Merigan and I prepared a second abstract describing the assay. We presented this abstract at the Sixth International AIDS Conference in San Francisco in 1990, listing Cetus scientists Alice Wang, Clayton Casipit, Mike Konrad, and Eric Groves, as well as Stanford researchers Sohini Sengupta, David Katzenstein, and David Schwartz, as co-authors. I presented the abstract at the AIDS conference in San Francisco in June 1990. A copy of that abstract is attached to the Rhyu Declaration as Exhibit 699.

22. By May of 1990, I had prepared a manuscript detailing the quantitative assay for HIV RNA in patient serum. I forwarded that manuscript to Eric Groves at Cetus for his review prior to submitting it. The manuscript was published with Cetus's consent in the *Journal of Infectious Diseases*, 163(4): 862-66, in April 1991 under the title *Detection and Quantification of Human Immunodeficiency Virus RNA in Patient Serum by Use of the Polymerase Chain Reaction*. ("JID article.") The article lists Cetus scientists Alice Wang, Clayton Casipit, Mike Konrad and Eric Groves as co-authors. This publication is discussed in the disclosure of the Merigan patents. A copy of that manuscript is attached to the Rhyu Declaration as Exhibit 1. Based on Cetus' consent to publish the JID article and the two earlier abstracts, I concluded that

the work done on the assay was within the public domain.

23. Around the same time period, I discussed with Dr. Merigan and other scientists at both Stanford and Cetus a phenomenon involving the inhibition of PCR reactions by heparin. In collaboration with Cetus scientists, including Sue Kim, a technician at Cetus, we verified this inhibitory effect. Cetus never asked me to keep the heparin work confidential. In July 1990, with Cetus' consent, we submitted a manuscript describing this research to the Journal of Clinical Microbiology. This work was published under the title *Inhibition of Human Immunodeficiency Virus Gene Amplification by Heparin,* Journal of Clinical Microbiology, 29(4):676-79 (1991) ("JCM article"). A copy of that manuscript is attached to the Rhyu Declaration as Exhibit 13.

24. I stopped visiting Cetus on a regular basis in October or November of 1989. I subsequently made only a handful of visits to Cetus, primarily to complete the work on the PCR assay and heparin inhibition. The *JID* article and the *JCM* article represent the end of my joint work with Cetus.

25. In July 1990, following submission of the JID article, I began experiments to ascertain whether HIV RNA levels in patient serum or plasma samples would correlate with the effect of HIV treatment and would inform decisions regarding patient treatment. All of my research from July 1990 going forward was performed at Stanford .

26. While the methods for evaluating the effect of anti-HIV therapy described in the monitoring

patents involve using a quantitative PCR assay, the PCR method itself is not the invention claimed in the patents.

27. Despite our work on the HIV RNA quantitation assay, it was quite unclear in mid 1990 whether the quantitation technique would work reliably to detect responses to antiviral therapy. For example, there was widespread uncertainty at the time about whether the assay be sufficiently sensitive and reproducible to measure HIV RNA changes over time in a clinical setting. It was unclear whether the variability of virus levels and changes in virus levels for different individuals would be detectable using this assay. There was much uncertainty in the field about whether nucleic acid levels in plasma could be used to predict the effectiveness of the therapy. There was also an overriding concern about whether the available treatments would be strong enough to produce changes that could be measured.

28. In addition to the uncertainties described above, there were a number of factors that had not yet been worked out. Appropriate patient samples needed to be identified and obtained. The quantitative assay needed more refinement to improve sensitivity and reproducibility, Further improvements were made to the process of HIV RNA extraction from patient samples. We performed experiments to establish that samples could be stored for prolonged periods of time without degradation of HIV RNA. The assay then had to be performed in parallel with tests that could independently verify the effect of treatment. Statistical analyses had to be performed on the results obtained from the patient samples to determine whether there

was, in fact, a correlation between the effectiveness of treatment and HIV levels.

29. Drs. Merigan, Katzenstein, and I designed and carried out these experiments, with some assistance from Dr. Dennis Israelski, who provided patient samples. Cetus was not involved in any stage of the effort to design or carry out these clinical experiments. We designed the original experiments to test samples from patients who had been treated with a drug called dideoxyinosine, both by itself and in combination with AZT. Drs. Merigan, Katzenstein, and I worked on this through the summer and winter of 1990. By early 1991, we had demonstrated a correlation between HIV levels and the effectiveness of treatment.

30. In May 1991, Drs, Merigan, Katzenstein, Israelski, and I submitted a manuscript to the Journal of the Clinical Investigation (JCI) describing our findings. The article, *Reduction in Plasma Human Immunodeficiency Virus Ribonucleic Acid after Dideoxynucleoside Therapy as Determined by the Polymerase Chain Reaction,* Journal of Clinical Investigation, 88(5):1755-59 ("JCI article"), was published in November 1991. The article reports that a correlation could be made between the effect of anti-HIV therapy and HIV RNA level, enabling the use of the correlation to make therapeutic decisions for treating AIDS patients. The work described in the JCI article is the central work on which the monitoring patents are based.

31. Based on the fact that the JCI manuscript was received by the journal on May 14, 1991, I am confident that the substantive work reported in the

article was completed before April 19, 1991. It would have taken me at least a month and likely two months from the time I completed the experiments to write the manuscript, distribute the manuscript to my coauthors for their comments, to incorporate their comments, and to prepare the final manuscript and figures for submission.

32. Since 1989, I have had interactions with John Sninsky at conferences and scientific meetings. We have discussed the method of monitoring the effectiveness of HIV therapy using PCR on numerous occasions. He has never indicated to me that he believed that Cetus deserved any credit for this work. He has never indicated to me that he believed that Cetus or Roche had any ownership interest in this work.

33. Prior to this suit, no one else at Cetus or Roche communicated to me that they believed the work described in the *JCI* article should be attributed to Cetus or Cetus' scientists.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this declaration was executed in Palo Alto, California on October 27, 2006.

/s/ Mark Holodniy

Mary Holodniy M.D.

APPENDIX I

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION

Case No. C 05 04158 MHP

[Filed October 27, 2006]

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiff,

v.

ROCHE MOLECULAR SYSTEMS, ET AL.,

Defendants.

ROCHE MOLECULAR SYSTEMS, ET AL.,

Counterclaimants,

v.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY: THOMAS MERIGAN AND MARK HOLODNIY

Counterclaim Defendants.)
)

DECLARATION OF LUIS R. MEJIA IN SUPPORT OF COUNTERCLAIM DEFENDANTS STANFORD UNIVERSITY, DR. MERIGAN AND DR. HOLODNIY'S MOTION FOR SUMMARY JUDGMENT

I, LUIS R. MEJIA, declare:

1. I am a Senior Licensing Associate in the Office of Technology Licensing at Stanford University, which is plaintiff in the current case. I have knowledge of the following, and if called as a witness, I could and would testify competently to this declaration's contents.

2. In this declaration, I refer to exhibits which I understand will be submitted as attachments to the attorney Declaration of Michelle S. Rhyu.

3. As Senior Licensing Associate at Stanford, my job responsibilities include: (1) discussing potential inventions with inventors; (2) reviewing invention disclosure statements submitted by inventors; (3) communicating with outside counsel regarding patent prosecution or litigation related to Stanford's intellectual property; (4) assessing inventions, patent applications and patents for potential economic value; (5) seeking and negotiating licenses to intellectual property; and (6) corresponding with the Office of Sponsored Research (formerly the "Sponsored Projects Office"), with respect to government grants and contracts. These were also my duties in the 1989-1992 time frame. As a function of my position, I am familiar

with Stanford's current policies relating to inventions, as well as its policies in the 1980s and 1990s.

4. I am aware of the work that Drs. Thomas Merigan, Mark Holodniy, David Katzenstein, and Mark Kozal performed that is described in their patents, U.S. Patent Nos. 5,968,730 (the "'730 patent"), 6,503,705 (the "'705 patent"), 5,631,128 ("'128 patent"); 5,856,086 ("'086 patent"), 5,650,268 ("'268 patent"), and Reissue Patent No. RE38,352 E ("'352 patent"). I am also aware that there is a pending application corresponding to the publication US20031018986 A1. I note that publication US20110018181 A1 corresponds to the '705 patent. Collectively, I will refer to all of these patents and applications as the "Merigan patents."

5. The Merigan patents all stem from an original patent application, No. 071883,327 ("'327 application"), which was filed on May 14, 1992. Based on the disclosure in this application, the '268 patent issued on July 22, 1997; the '730 patent issued on October 19, 1999, and the '705 application issued on January 7,2003. The pending application is also based on the disclosure in the '327 application. A "continuation-in-part" of the '327 application was filed on August 15, 1994, adding more information to the original disclosure. Based on the continuation-in-part, the '128 patent issued on May 20, 1997, the '086 patent issued on January 5, 1999, and the '352 Reissue patent issued on December 16, 2003.

6. The original '327 application first became publicly available upon issuance of the '268 patent in 1997. That application has claims for monitoring the effectiveness of anti-HIV treatment by detecting HIV

nucleic acids using PCR. A copy of the patent application is attached to the Rhyu Declaration as Exhibit 692 at STAN 014837-843.

7. In 1992, I was the person responsible for this application within the Office of Technology Licensing.

8. I understand that the research performed and the inventions described in the Merigan patents were all funded by at least two U.S. government grants: (1) the Center for AIDS Research grant AI-27762, and (2) AIDS Clinical Trial Group ("ACTG") Grant AI-27766. Both grants were issued by the National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID).

9. In the 1990s, I was engaged in seeking licensees to the inventions in these patents. For example, beginning in the spring of 1998, I sent a series of letters to Tom MacMahon of the Laboratory Corporation of America (LabCorp) to offer a license to the '128 and '268 patents. I sent a letter to Mr. MacMahon dated October 1, 1998 to follow up on my prior inquiries about LabCorp taking a license. A copy of the letter is attached to the Rhyu Declaration as Exhibit 554A.

10. After the '730 patent issued in 1999, I specifically sought to license this technology to Roche. On or about April 6, 2000, I went to Roche in Basel, Switzerland, and made a presentation to Claude Montandon and Andreas Maurer, Roche's then Director of Licensing. The presentation included slides, which I presented at that meeting. A copy of those slides is marked as Exhibit 693 in the Rhyu declaration. During that meeting, I referred to the

work that the Stanford inventors had done with Cetus and had published in the *Journal of Infectious Diseases* in April 1991. A copy of that article is attached to the Rhyu Declaration as Exhibit 1. I also discussed in that meeting Stanford's view that Cetus did not appreciate the value of quantification of HIV RNA in plasma until at least June 1992. I discussed the article published by Drs. Merigan, Katzenstein, Holodniy, and Israelski in the November 1991 issue of the *Journal of Clinical Investigation*. The article is attached to the Rhyu declaration as Exhibit 46. I also discussed in that meeting Stanford's view that Drs. Merigan, Katzenstein and Holodniy had conceived the idea that the measurement of HIV RNA from plasma could be useful for assessing efficacy of antiviral therapy. I further discussed the therapy monitoring invention in the '730 patent.

11. I concluded the April 2000 meeting by offering Roche an exclusive license to the '730 patent and related Stanford patents. Through my presentation, it was clear that Stanford did not recognize that either Cetus or Roche had any ownership or license interest in the Merigan patents.

12. Prior to and during the April 2000 meeting, no one from Roche ever indicated to me that Roche believed it had any right of ownership or license to the Merigan patent family.

13. At no time prior to this suit has Roche indicated to me or the Office of Technology Licensing that it was exercising an option to an exclusive license to the invention in the Merigan patents, or that it was exercising an option to a nonexclusive license. It is my

understanding that Roche has never had any license to the inventions in the Merigan patents.

14. Stanford has undertaken substantial efforts to license the inventions of the Merigan patents to third parties and has participated in two significant patent litigations relating to the patents.

15. Stanford's Policy on Inventions, Patents, and Licensing that was in effect in the 1980s is reflected in Exhibits 24 and 25, attached to the Rhyu declaration. According to that policy, Stanford allowed rights in inventions to remain with inventors "if possible." However, the policy recognized that "the great majority" of inventions arose from research that was externally funded and covered by those external funding agreements. (*See* Exh. 24, ¶ 1 .) In the case of government-funded research, distribution of rights in the invention was governed by the Bayh-Dole Act.

16. Within the Office of Technology Licensing, the Bayh-Dole Act is understood to grant the University the first right to retain title to an invention that was made with government grants. If the University does not elect to retain title, and the inventor wishes to obtain rights in the invention, the inventor must petition the granting agency for permission to retain rights in the invention. Only after the government consents can the inventor obtain ownership of the invention.

17. Consistent with the Bayh-Dole Act, Stanford required employees to assign to Stanford their interests in inventions that had been supported by U.S. government grants. The Stanford Copyright and Patent Agreement, Exhibit 23, paragraph 2, sets forth

this obligation. A copy of the agreement is attached to the Rhyu Declaration as Exhibit 23.

18. According to the Stanford policy, Stanford had the first right to have title in the Merigan patents. Stanford exercised that right and the inventors have assigned the patents to Stanford.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this declaration was executed in Palo Alto, California on October 26, 2006.

/s/ Luis R. Mejia
LUIS R. MEJIA

APPENDIX J

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION

Case No. C 05 04158 MHP

[Filed December 1, 2006]

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Plaintiff, v. ROCHE MOLECULAR SYSTEMS, ET AL., Defendants.	)
ROCHE MOLECULAR SYSTEMS, ET AL., Counterclaimants, v. THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY; THOMAS MERIGAN AND MARK HOLODNIY	)

Counterclaim Defendants.)
)

SUPPLEMENTAL DECLARATION OF LUIS R. MEJIA IN SUPPORT OF STANFORD UNIVERSITY, DR. MERIGAN AND DR. HOLODNIY'S OPPOSITION TO DEFENDANTS' MOTION TO STRIKE

I, LUIS R. MEJIA, declare:

1. I am a Senior Licensing Associate in the Office of Technology Licensing ("OTL") at Stanford University. I previously submitted a declaration dated October 26, 2006, in support of Stanford University, Dr. Merigan, and Dr. Holodniy's Motion for Summary Judgment. (Docket No. 94.) I have knowledge of the following, and if called as a witness, I could and would testify competently to this declaration's contents.

2. My October 26, 2006 declaration generally describes my relevant responsibilities, duties, and experience at my position in the OTL. (Docket No. 94, ¶¶ 3-8.) Stated more specifically, my responsibilities included receiving information about government grants that funded inventions and verifying that those grants were issued to the appropriate laboratories.

3. As I previously stated, in 1992, I was the person responsible for managing the applications leading to the patents at issue in this lawsuit. On April 9, 1992, Dr. Merigan submitted an invention disclosure relating to the work that was ultimately included in these applications. (Docket No. 110, Ex. 6.) Dr. Merigan identified in the invention disclosure that the work was sponsored by "NIH," which I understood to

be the National Institutes of Health. (*Id.*) Dr. Merigan further identified in that disclosure that the work was funded by U.S. government grants Nos. AI27762-04 and AI277666-07. (*Id.*) It was then and remains OTL's pattern and practice to verify by reference to a Stanford grants database that the grants cited by inventors correspond to issued, current grants. According to this pattern and practice, at or near the time the disclosure was submitted, I, or someone working under my direction, would have verified that the grant numbers listed in the April 9, 1992 invention disclosure corresponded to existing grants applicable to Dr. Merigan. This practice is important, because the Bayh-Dole Act requires the University to report any inventions made with government funds to the government. According to this Act and Stanford policy, it is OTL's and my responsibility to identify government-funded inventions and to notify the government as to whether Stanford elects to retain title to the invention. (*See* Docket No. 94, ¶¶ 71 15-18.)

4. As part of my duties and responsibilities, I have personal knowledge of Exhibits 710, 711, and 712, which were attached to the Supplemental Declaration of Michelle S. Rhyu in Support of Counterclaim Defendants Stanford University, Dr. Merigan and Dr. Holodniy's Opposition to Counterclaimant RMS's Motion for Summary Judgment. (Docket No. 113.)

5. Exhibit 710 contains true and correct copies of correspondence from the OTL to employees of the National Institutes of Health, notifying the NIH that the University elects to retain title to the inventions of the original invention disclosure. I received a copy of each piece of correspondence contained in Exhibit 710. The correspondence in Exhibit 710 was created at or

near the listed dates as a regularly conducted business activity of the OTL by either myself or someone working under my direction, such as Eric Danly. I had knowledge of the correspondence and the matters set forth therein at or near their dates. This correspondence was maintained by the OTL in the course of its regularly conducted business activity.

6. Exhibit 711 contains a true and correct copy of a confirmatory nonexclusive license granted by Stanford to the United States Government to U.S. Patent Application Serial No. 07/883,327, in accordance with the University's obligations under the Bayh-Dole Act. The license in Exhibit 711 was created at or near the listed date as a regularly conducted business activity of the OTL by Katherine Ku. I had knowledge of the license and the matters set forth therein at or near its date. This license was maintained by the OTL in the course of its regularly conducted business activity.

7. Exhibit 712 contains a true and correct copy of a PTO Form 1619A recording the confirmatory license from Exhibit 711 with the U.S. Patent and Trademark Office and a copy of the license. Exhibit 712 is a certified PTO record that Stanford obtained from the ReedFax service. The documents in Exhibit 712 were created at or near the listed dates as a regularly conducted business activity of the OTL by its personnel or on their behalf. I had knowledge of these documents and their contents at or near their dates.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this declaration was executed in Palo Alto, California on December 1, 2006.

/s/ Luis R. Mejia
LUIS R. MEJIA

APPENDIX K

Copyright and Patent Agreement
STANFORD UNIVERSITY

I understand that Stanford University ("Stanford") enters into agreements ("Contracts or Grants") with third parties including the United States Federal Government ("Sponsors") and establishes policies ("Policies") which impose and set forth certain obligations and requirements with respect to rights in copyrightable materials and inventions.

Now, therefore, in consideration of my employment or continued employment by Stanford, the receipt of remuneration from Stanford, participation in projects administered by Stanford, access to or use of facilities provided by Stanford, and/or other valuable consideration, I hereby agree as follows:

1. If I perform work and create copyrightable materials or conceive or first actually reduce to practice any invention (whether or not it may be considered patentable) under or in the course of an Contract or Grant, I will provide Stanford promptly at the Sponsored Projects Office (Intellectual Property Administration):

(a) with respect to such copyrightable materials, such copies and information as may be requested by Stanford to fulfill its obligations under Contracts or Grants, and

(b) with respect to such invention, a written disclosure sufficient fully to disclose the invention and to obtain patent protection thereon.

2. I agree to assign or confirm in writing to Stanford and/or Sponsors that right, title and interest in and to such copyrightable materials, including associated copyright, and such inventions as required by Contracts or Grants, and to execute and to deliver all documents and to do any and all things necessary or proper on my part to enable Stanford to comply with any Contracts or Grants relating to such copyrightable works and such inventions.

3. I agree to waive any claim or rights to any pecuniary award or compensation under the provisions of the Atomic Energy Acts of 1946 or 1954 with respect to any invention I make under or in the course of a Contract or Grant requiring such waiver.

4. If I perform work and create copyrightable materials under a project commissioned by Stanford or otherwise identified in Policies as involving copyright obligations to Stanford, I agree to assign or confirm in writing to Stanford that right, title and interest in and to such copyrightable materials, including associated copyright, required by Stanford in accordance with Policies.

5. I am now under no consulting or other obligations to any third person, organization or corporation in respect to rights in copyrightable materials or inventions which are, or could reasonably be construed to be, in conflict with this agreement.

6. I will not enter into any agreement creating copyright or patent obligations in conflict with this agreement.

7. This agreement shall apply to all copyrightable materials created, and to all inventions made, conceived or first actually reduced to practice after the date of execution hereof, and shall be binding on myself, my estate, heirs and assigns.

Signed this 28 day of June, 1988

/s/ Mark Holodniy
Signature

MARK HOLODNIY
Typed or printed name

FELLOW
Title (e.g., professor, student, visiting scientist, etc.

INFECTIOUS DISEASE
Department

[redacted]
Social Security No.

Luzmarie Vallejo
Signature of witness

LuzmArie VAllejo
Typed or printed name of witness

NOTICE: This Agreement does not apply to an Invention which qualifies fully under Labor Code Section 2870 (i.e., an invention for which no Stanford University equipment, supplies, facility, or trade-secret information was used and which was developed entirely on employee's own time and (a) does not relate to Stanford research or (b) does not result from any work performed by employee for Stanford).

See University Guide series 75 and 76 for instructions and information

SIGNER

APPENDIX L

EG → M. Konrad
2/14/89

VISITOR'S CONFIDENTIALITY AGREEMENT

In consideration of Cetus Corporation and its subsidiaries (herein "CETUS") granting me access to CETUS' facilities and information, I hereby agree as follows:

1. Acting as a consultant and an independent contractor, I will be learning from Dr. Eric Groves and Dr. Michael Konrad of CETUS techniques in molecular biology and Polymerase Chain Reaction assays.

   I will be at CETUS from January 15, 1989, through July 1, 1989. During the term of this Agreement, I agree not to perform consulting services in any area involving microbial genetics for any company, corporation, institution, or commercial enterprise (other than affiliates of CETUS).

2. I may have access to and acquire techniques, know-how, or other information of a confidential nature concerning CETUS' experimental and developmental work, trade secrets, secret procedures, business matters or affairs including, but not limited to, information relating to ideas, discoveries, inventions, disclosures, processes, methods, systems, formulas, patents, patent

applications, machines, materials, research plans and activities, research results, and business marketing information, plans, operations, activities, and results. I WILL NOT DISCLOSE ANY SUCH INFORMATION TO ANY PERSON OR ENTITY OR USE ANY SUCH INFORMATION WITHOUT CETUS' PRIOR WRITTEN CONSENT. Information shall, for purposes of this Agreement, be considered to be confidential if not known in the field generally, even though such information has been disclosed to one or more third parties pursuant to joint research agreements, consulting agreements, or other entered into by CETUS or any of its affiliates. Excluded from the obligations of confidentiality and nonuse agreed to herein is information (i) that I can establish I knew prior to my acquiring it from CETUS; (ii) that I receive from a third party who, when providing it to me, is not under an obligation to CETUS to keep the information confidential; or (iii) that enters the public domain through no fault of mine.

3. If, as a consequence of my access to CETUS' facilities or information, I conceive of or make, alone or with others, ideas, inventions and improvements thereof or know-how related thereto that relate in any manner to the actual or anticipated business of CETUS, I will assign and do hereby assign to CETUS, my right, title, and interest in each of the ideas, inventions and improvements thereof described in this paragraph. I will, at CETUS' expense, execute, acknowledge, and deliver such documents as are necessary or desirable for vesting in CETUS all rights assigned to it under the foregoing sentence.

4. If any provision of the Agreement is held to be unenforceable for any reason, such provision shall be adjusted rather than voided, if possible, in order to achieve the intent of the parties to the extent possible. In any event, all other provisions of this Agreement shall be deemed valid and enforceable to the full extent possible.

/s/ Mark Holodniy MD
Signature

MARK HOLODNIY, M.D.
Printed Name

2/14/89
Date

STANFORD UNIVERSITY MEDICAL CENTER
Address DIVISION OF INFECTIOUS DISEASE

stan.ca

APPENDIX M

United States Patent

Patent Number: US 5968730

Document Type: Utility

Title: POLYMERASE CHAIN REACTION ASSAYS FOR MONITORING ANTIVIRAL THERAPY AND MAKING THERAPEUTIC DECISIONS IN THE TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME

Issue Date: October 19, 1999 (19991019)

Inventor(s): Merigan, Thomas C. (Portola Valley, CA); Katzenstein, David A. (Menlo Park, CA); Holodniy, Mark (Mountain View, CA)

Patent Assignee: Leland Stanford Junior University (Palo Alto, CA)

. . . .

ABSTRACT:

The present invention relates to methods of monitoring, via polymerase chain reaction, the clinical progression of human immunodeficiency virus infection and its response to antiretroviral therapy. According to the invention, polymerase chain reaction assays may be used to predict immunological decline

and to identify, at an early stage, patients whose infection has become resistant to a particular antiretroviral drug regimen.

. . . .

This application is a divisional application of U.S. application Ser. No. 07/883,327, filed May 14, 1992, now abandoned which is incorporated herein by reference in its entirety.

This invention was made with Government support under contracts AI27762-04 and AI27766-07 awarded by the National Institutes of Health. The Government has certain rights in this invention.

APPENDIX N

United States Patent

Patent Number: US 6503705 B2

Document Type: Utility

Title: POLYMERASE CHAIN REACTION ASSAYS FOR MONITORING ANTIVIRAL THERAPY AND MAKING THERAPEUTIC DECISIONS IN THE TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME

Issue Date: January 7, 2003 (20030107)

Inventor(s): Kozal, Michael J. (Menlo Park, CA); Merigan, Thomas C. (Portola Valley, CA); Katzenstein, David A. (Menlo Park, CA); Holodniy, Mark (Mountain View, CA)

Patent Assignee: Leland Stanford Junior University (Palo Alto, CA)

. . . .

ABSTRACT:

The present invention relates to methods of monitoring, via polymerase chain reaction, the clinical progression of human immunodeficiency virus infection and its response to antiretroviral therapy. According to the invention, polymerase chain reaction

assays may be used to predict immunological decline and to identify, at an early stage, patients whose infection has become resistant to a particular antiretroviral drug regimen.

. . . .

This application is a continuation application of U.S. Ser. No. 09/399,082, filed Sep. 17, 1999, now abandoned, which is a continuation application of U.S. Ser. No. 08/470,855, filed Jun. 6, 1995, now U.S. Pat. No. 5,968,730, which is a divisional application of U.S. Ser. No. 07/883,327 filed May 14, 1992, now abandoned, all of which are incorporated herein by reference in their entirety.

This invention was made with Government support under contracts AI27762-04 and AI27766-07 awarded by the National Institutes of Health. The Government has certain rights in this invention.

APPENDIX O

UNITED STATES PATENT
AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	:	6,503,705 B2	Page 1 of 1
DATED	:	January 7, 2003	
INVENTOR(S)	:	Thomas C. Merigan, David A. Katzenstein and Mark Holodniy	

It is certified that error appears in the above identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [75], Inventors, delete "**Michael J. Kozal**, Menlo Park, CA (US);"
Item [74], *Attorney, Agent or Firm*, please replace "Howrey Simon Arnold & White, Ltd." with -- Howrey Simon Arnold & White, LLP --

Column 12,
Line 48, please insert a period after "patients" and capitalize "only" to read as follows:
-- patients. Only 7 of 23 were plasma virus positive by culture --

Signed and Sealed this

Seventeenth Day of June, 2003

/s/ James Rogan
JAMES E. ROGAN
Director of the United States
Patent and Trademark Office

APPENDIX P

United States Patent

Patent Number: US 7129041 B2

Document Type: Utility

Title: POLYMERASE CHAIN REACTION ASSAYS FOR MONITORING ANTIVIRAL THERAPY AND MAKING THERAPEUTIC DECISIONS IN THE TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME

Issue Date: October 31, 2006 (20061031)

Inventor(s): Merigan, Thomas C. (Portola Valley, CA); Katzenstein, David A. (Menlo Park, CA); Holodniy, Mark (Mountain View, CA)

Patent Assignee: The Board of Trustees of the Leland (Stanford Junior University Palo Alto, CA)

. . . .

ABSTRACT:

The present invention relates to methods of monitoring, via polymerase chain reaction, the clinical progression of human immunodeficiency virus infection and its response to antiretroviral therapy. According to the invention, polymerase chain reaction assays may be used to predict immunological decline

and to identify, at an early stage, patients whose infection has become resistant to a particular antiretroviral drug regimen.

. . . .

This application is a divisional application of U.S. Ser. No. 09/782,971, filed Feb. 13, 2001 now U.S. Pat. No. 6,503,705, which is a continuation application of U.S. Ser. No. 09/399,082 filed Sep. 17, 1999, abandoned, which is a continuation application of U.S. Ser. No. 08/470,885, filed Jun. 6, 1995, now U.S. Pat. No. 5,968,730, which is a divisional application of U.S. Ser. No. 07/883,327, filed May 14, 1992, abandoned. All of these applications and patents are incorporated herein by reference in their entirety. This invention was made with Government support under contracts A127762-04 and A127766-07 awarded by the National Institutes of Health. The Government has certain rights in this invention.

APPENDIX Q

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

Case No. C 05 04158 MHP

[Dated November 15, 2006]

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiff,

v.

ROCHE MOLECULAR SYSTEMS, ET AL.,

Defendants.

ROCHE MOLECULAR SYSTEMS, ET AL.,

Counterclaimants,

v.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY; THOMAS MERIGAN AND MARK HOLODNIY

Counterclaim Defendants.)
)

SUPPLEMENTAL DECLARATION OF MICHELLE S. RHYU IN SUPPORT OF COUNTERCLAIM DEFENDANTS STANFORD UNIVERSITY, DR. MERIGAN AND DR. HOLODNIY'S OPPOSITION TO COUNTERCLAIMANT RMS'S MOTION FOR SUMMARY JUDGMENT

I, Michelle S. Rhyu, declare as follows:

1. I am an attorney with the law firm of Cooley Godward Kronish LLP, counsel of record for The Board of Trustees of the Leland Stanford Junior University and Thomas Merigan in the above-captioned matter. I have knowledge of the following, and if called as a witness, I could and would testify competently to this declaration's contents.

* * *

4. Attached hereto as Exhibit Q is a true and correct copy of excerpts from the deposition of Michael S. Ostrach, conducted on August 21, 2006.

* * *

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this declaration was executed at Palo Alto, California on November 15, 2006.

/s/
Michelle S. Rhyu

Exhibit Q

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

Case No. C 05-04158 MHP

[Taken August 21, 2006]

THE BOARD OF THE TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Plaintiff, vs. ROCHE MOLECULAR SYSTEMS, INC.; ROCHE DIAGNOSTICS CORPORATION; ROCHE DIAGNOSTICS OPERATIONS, INC.; ROCHE DIAGNOSTIC SYSTEMS, INC. Defendant.	)
AND RELATED COUNTERCLAIM.	)

HIGHLY CONFIDENTIAL – ATTORNEYS' EYES ONLY – RESTRICTED
VIDEOTAPED DEPOSITION
OF MICHAEL S. OSTRACH
San Francisco, California
Monday, August 21, 2006

Reported by:
SUZANNE F. BOSCHETTI
CSR No. 5111

Job No. 3-51840

* * *

[p.57:18-25]

Q. Do you recall any exceptions to the general policy of providing rights to professors --

A. I don't recall --

Q. -- in the Stanford policy?

A. -- a specific exception. I would be -- expect that government-funded inventions might be dealt with specifically and possibly differently.

Q. Why would you have that expectation?

[p.58:1-22]

A. Because I think until before 1984, the government claimed an interest in inventions made on its grants and in '84 the law was changed to provide a grant to the institution of those rights, which I would expect, therefore, would then be provided to the professor consistent with other patent rights. But before '84, and since this is right around '84, as I recall, don't know.

Q. Now, why do you say that you -- let me back up a little bit.

So in 1984, what was your understanding of way in which the law was changed with respect to intellectual property arising from grants?

MR. BOOZELL: Calls for a legal conclusion. Calls for speculation. Lacks foundation. Incomplete hypothetical. Calls for an expert opinion.

THE WITNESS: I thought it was '84 that the Bayh-Dole Act was passed, where Congress provided that inventions made on federal grants could be given to the university rather than kept by the government. I -- I believe before that the university sort of had to ask the government to give it the patents.

* * *

OPPOSITION BRIEF

161

(5)

Supreme Court, U.S.
FILED
MAY 26 2010
OFFICE OF THE CLERK

No. 09-1159

IN THE

Supreme Court of the United States

BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY,
Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., *et al.*,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF IN OPPOSITION

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Counsel for Respondents

May 26, 2010

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D.C. 20002

QUESTION PRESENTED

Whether the Bayh-Dole Act permits a private university to void, unilaterally and retroactively, an inventor's otherwise valid contractual assignment of his rights in an invention, solely because that invention was developed in part with federal funds.

CORPORATE DISCLOSURE STATEMENT

Pursuant to the Court's Rule 29.6, Respondents state as follows:

1. Roche Molecular Systems, Inc., a Delaware corporation, is a wholly-owned subsidiary of Roche Holdings, Inc., a Delaware corporation, which is a subsidiary of Roche Finance Ltd, which is a subsidiary of Roche Holding Ltd. More than 10% of Roche Holding Ltd's voting shares are held by Novartis International Ltd (Switzerland) as direct holder, with its parent Novartis AG (Switzerland) as economic beneficiary.

2. Roche Diagnostics Corporation, an Indiana corporation, is a wholly-owned subsidiary of Roche Holdings, Inc.

3. Roche Diagnostics Operations, Inc., a Delaware corporation, is a wholly-owned subsidiary of Roche Diagnostics Corporation.

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IN THE

Supreme Court of the United States

No. 09-1159

BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY,
Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., *et al.*,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF IN OPPOSITION

INTRODUCTION

Stanford University's petition for certiorari is defective in numerous ways. First and foremost, this case does not present the very question on which Stanford seeks this Court's review. Contrary to its assertion, Stanford's rights in the patents-in-suit have not been "terminated" (Pet. i); rather, Stanford co-owns the patents through assignments from two of the three co-inventors. Nor does this case raise important issues bearing on Stanford's or the federal government's rights under the Bayh-Dole Act, 35 U.S.C. §§ 200 *et seq.* Rather, this case involves the factbound and splitless application of settled principles of contract interpretation to contract language

in an atypical factual situation, namely where an invention is conceived at a startup company and later confirmed by work done at a large university that receives federal funds. This fact pattern is unlikely to recur, notwithstanding the insistence of Stanford and its chorus of *amici*. In fact, this Court's review is unlikely to alter the outcome even in *this* case, as the district court held the patents invalid for obviousness, a fact Stanford does not even mention.

Moreover, Stanford's petition is meritless. As the court of appeals held, the Bayh-Dole Act nowhere alters an inventor's basic freedom to assign his own rights in an invention to a third party. The Act achieves its laudable goals by regulating the relationship between the federal government and entities that receive federal grant money. The inventor in this case assigned his rights as part of a collaboration between Stanford and a private company. Stanford shows no reason to believe that it can renege retroactively on contractual commitments voluntarily assumed by its agents. The petition should be denied.

STATEMENT

A. Cetus's Groundbreaking Research

This case has its roots in groundbreaking research conducted in the 1980s at Cetus Corporation, a startup company based in California. One Cetus employee, Dr. Kary Mullis, discovered an important technique known as polymerase chain reaction, or PCR, which allows scientists "to make billions of copies of specific sequences of DNA from a small number of starting molecules." Pet. App. 32a. The PCR technique also enables scientists to investigate and manipulate DNA. The technique is instrumental

in current medical and biological applications such as gene cloning, diagnosis of hereditary diseases, detection of infectious diseases and forensic crime scene analysis. For this discovery, Dr. Mullis won the 1993 Nobel Prize in Chemistry. *Id.*

B. Stanford Sends Its Scientists To Learn From Cetus

In 1985, Cetus scientists began looking for ways to use PCR to detect and quantify the presence of human immunodeficiency virus (HIV) in blood. Pet. App. 32a. Scientists at major universities sought out Cetus for its know-how and expertise in this area. One such scientist was Dr. Thomas Merigan, the director of the Center for AIDS Research at Stanford University. *Id.* Over the course of his collaboration with Cetus, involving investigation of HIV and the testing of experimental anti-HIV drugs, Dr. Merigan executed several "Materials Transfer Agreements" (MTAs) with Cetus that gave Dr. Merigan the right to use Cetus's proprietary materials and information "in exchange for a non-exclusive, royalty-free license to Cetus for any intellectual property developed as a result of the MTA." Pet. App. 33a. In February 1989, to support Dr. Merigan's work in the HIV arena, Stanford (along with Dr. Merigan) signed a similar MTA agreement with Cetus, promising Cetus "the first option to an exclusive license, at a reasonable royalty to be negotiated in good faith ... or at CETUS' option, a nonexclusive license." Pet. App. 34a.

In February 1989, Dr. Merigan sent his research fellow, Dr. Mark Holodniy, to Cetus "in order to explore the use of PCR techniques in his work." Pet. App. 34a. Dr. Holodniy had no previous PCR experience. Pet. App. 34a-35a. In order to have access to

Cetus scientists and materials, Dr. Holodniy signed a Visitor Confidentiality Agreement (VCA), which provided:

> If, as a consequence of my access to CETUS' facilities or information, I conceive of or make, alone or with others, ideas, inventions and improvements thereof or know-how related thereto that relate in any manner to the actual or anticipated business of CETUS, *I will assign and do hereby assign to CETUS*, my right, title, and interest in each of the ideas, inventions and improvements thereof described in this paragraph.

Pet. App. 35a-36a (quoting VCA) (emphasis added).

Dr. Holodniy had previously signed a Copyright and Patent Agreement (CPA) with Stanford. Pet. App. 4a. The CPA did not contain a present assignment of rights, but only stated: "*I agree to assign or confirm in writing* to Stanford and/or Sponsors that right, title and interest in . . . such inventions as required by Contracts or Grants." Pet. App. 13a (emphasis added by court of appeals).

After signing the VCA, Dr. Holodniy "began commuting daily to Cetus," "was assigned a lab bench in Cetus' Clinical Group, and had access to Cetus personnel, materials, and equipment." Pet. App. 35a. Dr. Holodniy spent approximately nine months at Cetus, "receiving technical information from Cetus scientists and proprietary physical materials from Cetus." Pet. App. 36a.

C. The Inventive PCR Assay Is Conceived At Cetus

The invention at issue in this case is "an assay for quantitating HIV RNA using PCR" consisting of five steps. Pet. App. 36a. Dr. Holodniy admitted that he "had never performed any of the five steps of the PCR assay for HIV prior to working at Cetus." Pet. App. 37a. In fact, Dr. Holodniy sought out the assistance of Cetus scientist Dr. Alice Wang to develop the methods needed to quantitate HIV. Pet. App. 36a. Cetus molecular biologist Clayton Casipit, working in Dr. Wang's lab, developed the critical material — a cRNA standard — that was used to create a standard curve to quantify HIV. Pet. App. 36a-37a. The Cetus scientists provided the cRNA standard to Dr. Holodniy in October 1989. Pet. App. 37a. As the district court found, the inventive assay was conceived at Cetus while Dr. Holodniy was resident there. Pet. App. 37a, 39a, 41a. Dr. Holodniy requested permission from Cetus to publish the assay and its results in two abstracts; Cetus granted permission after Dr. Holodniy added the names of Dr. Wang, Casipit and another Cetus scientist who had contributed to the assay. Pet. App. 37a. In April 1991, an article in the *Journal of Infectious Diseases* disclosed the assay, naming Dr. Holodniy as lead author and scientists from Cetus and Stanford as co-authors. Pet. App. 38a-39a.

Although Stanford claimed in litigation that the inventive assay was conceived at Stanford (*see, e.g.*, Pet. 12), Stanford refused to disclose when it believed the invention had been conceived (Pet. App. 58a n.7). The district court rejected Stanford's argument, finding as a matter of fact that the invention was

"conceived" and the assay "completed" before Dr. Holodniy left Cetus. Pet. App. 56a.

D. Stanford Continues The Research And Secretly Patents It

After Dr. Holodniy returned to Stanford, he, Dr. Merigan, and others continued to work on the PCR assay, conducting experiments "to correlate the detection of HIV nucleic acid levels via the PCR assays with the effectiveness of HIV treatment." Pet. App. 39a. Stanford has contended that it received federal funds through the National Institutes of Health for its research. Pet. App. 5a. However, Stanford has never disclosed the federal funding agreement that allegedly covers this work, and it has never demonstrated how Dr. Holodniy's work at Cetus, as well as the contributions of Cetus and its scientists, is connected to research grants awarded to Stanford.

In May 1992, Stanford filed a patent application entitled "Polymerase Chain Reaction Assays for Monitoring Antiviral Therapy and Making Therapeutic Decisions in the Treatment of Acquired Immunodeficiency Syndrome," directed to "correlating measurements of HIV nucleic acids obtained via a PCR assay with determining whether or not a therapy is effective." Pet. App. 31a. Stanford named as inventors Drs. Merigan and Michael Kozal, and later added Drs. Holodniy and David Katzenstein, all Stanford employees (Dr. Kozal was dropped from a continuation application). Pet. App. 3a-4a. Stanford did not name any Cetus scientists as co-inventors, nor did it inform Cetus that it had sought to patent the PCR assays. The application later led to issuance of the three related patents-in-suit, U.S. Patents Nos.

5,968,730 (issued in 1999), 6,503,705 (issued in 2003) and 7,129,041 (issued in 2006).

In 1995, Drs. Holodniy, Katzenstein and Merigan executed written assignments purporting to convey their interests in the patent application to Stanford. Pet. App. 41a. Stanford also informed the government that it "elected to retain title" to the inventions under the Bayh-Dole Act, 35 U.S.C. §§ 200-212. Pet. App. 5a-6a. However, Dr. Holodniy's interest in the patents had already been assigned to Cetus six years earlier through the VCA.

E. Stanford Sues Cetus's Successor, Roche, To Prevent Commercialization Of The Invention

In 1991, Roche acquired Cetus's PCR assets, including Cetus's rights under transferred contracts and confidentiality agreements. Pet. App. 5a. Roche began manufacturing HIV test kits that employ the PCR assays conceived at Cetus; the kits quantify HIV in an infected patient's blood and assist physicians in their treatment. *Id.* Roche first offered its test kits for sale in 1996, years before any of the patents-in-suit issued.

In 2005, after the patents-in-suit had issued and Roche's products had been on the market for nine years, Stanford sued Roche for infringement. Roche answered and counterclaimed on numerous grounds, including invalidity, lack of standing, ownership, and license.

F. The District Court Decisions

The district court ruled that the patented inventions were "conceived" and the assay "completed" by the time Dr. Holodniy left Cetus and that the method

of using PCR to monitor HIV treatment was "clear in the minds of Holodniy and the other Stanford scientists when the assay was completed at Cetus." Pet. App. 56a. The court found, however, that Roche's claim to ownership of the patents was barred by the statute of limitations and by laches. Pet. App. 49a, 51a.

Nonetheless, because the parties had briefed the issue of ownership in detail, the district court addressed it in the alternative. The court held that the invention's conception at Cetus "created an interest on the part of Holodniy in the patent applications" and that interest "was sufficient to trigger the assignment provision in the VCA." Pet. App. 57a. Accordingly, "[t]he VCA effectively assigned any rights that Holodniy had in the patented invention to Cetus." Pet. App. 59a.

The court stated, however, that the assignment "conflicted with the legal requirements of the Bayh-Dole Act, which mandated that Stanford be given a superior right to retain title to the patents." Pet. App. 62a. Because Stanford had allegedly obtained funds from the National Institutes of Health in connection with its research, Dr. Holodniy's assignment of the patents-in-suit was "void." Pet. App. 62a. The court also held that the licenses given by Stanford and Dr. Merigan to Cetus in 1988 and 1989 could not be transferred to Roche without Stanford's consent. Pet. App. 70a-72a.

The district court refused to certify its order for interlocutory appeal. Roche sought a writ of mandamus to vacate the district court's ruling; the court of appeals denied the writ as premature by a 2-1 vote. *In re Roche Molecular Sys., Inc.*, 516 F.3d 1003 (Fed. Cir. 2008).

Roche then moved for summary judgment that the patent claims were invalid for obviousness over, *inter alia*, the *Journal of Infectious Diseases* article co-authored by Stanford and Cetus scientists in April 1991. In a separate decision not reproduced in the appendix to Stanford's petition for certiorari, the district court held the patents invalid. *Bd. of Trs. of Leland Stanford Junior Univ.* v. *Roche Molecular Sys., Inc.*, 563 F. Supp. 2d 1016, 1049 (N.D. Cal. 2008).

G. The Court Of Appeals Decision

Stanford appealed the invalidity judgment to the Federal Circuit, and Roche cross-appealed the rejection of its ownership claim and its standing and license defenses. The court of appeals ruled that, although the district court had correctly dismissed Roche's counterclaim for patent ownership as time-barred, Roche was nonetheless allowed to assert ownership as a defense to infringement and to challenge Stanford's standing to sue. Pet. App. 11a-12a. The court of appeals noted that, under established principles of contract interpretation, the language "agree to assign" in Dr. Holodniy's CPA with Stanford reflected "a mere promise to assign rights in the future, not an immediate transfer of expectant interests." Pet. App. 13a (citing *IpVenture, Inc.* v. *Prostar Computer, Inc.*, 503 F.3d 1324, 1327 (Fed. Cir. 2007), and *Arachnid, Inc.* v. *Merit Indus., Inc.*, 939 F.2d 1574, 1580-81 (Fed. Cir. 1991)). Thus, while the CPA may have given Stanford "certain equitable rights against Holodniy," it did not give Stanford title to Dr. Holodniy's inventions. *Id.*

The VCA, by contrast, "effected a present assignment of Holodniy's future inventions to Cetus." Pet. App. 14a. Although Dr. Holodniy later effected a

present assignment to Stanford in 1995, "Cetus's legal title vested first . . . negating his subsequent assignment to Stanford during patent prosecution." *Id.* The court rejected Stanford's argument that it was a bona fide purchaser without notice of Dr. Holodniy's assignment (*see* 35 U.S.C. § 261), because Stanford was "charged with notice of its employees' assignments." Pet. App. 17a (citing authority under federal and California law); *see also* Pet. App. 64a (district court finding that Stanford had "imputed notice" of Dr. Holodniy's assignment).

The court of appeals rejected Stanford's reliance on the Bayh-Dole Act. The court observed that, while the Act allows the government to take title to federally-funded inventions, it does not indicate that title is "automatically forfeited." Pet. App. 19a (quoting *Cent. Admixture Pharmacy Servs., Inc.* v. *Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347, 1352-53 (Fed. Cir. 2007)) (internal quotation marks omitted). Rather, the Act provided the government with "at most, a discretionary option to [Dr. Holodniy's] rights." Pet. App. 19a. And nothing in the Act provided Stanford with the power to void a "prior, otherwise valid assignment[] of patent rights." *Id.* Rather, Stanford was entitled to claim "whatever rights were still available after the Government declined to exercise its option, including the rights of co-inventors Merigan, Katzenstein, and Kozal." *Id.* The court did not decide "whether Holodniy's execution of the VCA violated any provisions of the Bayh-Dole Act, or whether the Act provides the Government or Stanford some other legal recourse to recover Holodniy's rights." Pet. App. 20a n.1.

Because Stanford could not establish ownership of Dr. Holodniy's interest in the patents-in-suit, it lacked standing to sue Roche for infringement. Pet. App. 27a-28a. The court of appeals accordingly did not address the merits of the district court's decision holding the patent invalid; it simply vacated the judgment below and remanded with instructions to dismiss the case. Pet. App. 28a. The court denied Stanford's petition for panel rehearing and rehearing en banc. Pet. App. 76a-77a.

REASONS FOR DENYING THE PETITION

I. THE PETITION DOES NOT WARRANT THIS COURT'S ATTENTION

A. The Case Does Not Present The Issue On Which Stanford Seeks Review

Stanford asks this Court to decide whether its rights to the patented invention have been "terminated unilaterally" through Dr. Holodniy's voluntary assignment of his patent rights to Cetus. Pet. i. That question simply is not presented in this case.

Stanford remains a co-owner of the patents-in-suit by virtue of the assigned rights of the other co-inventors, Drs. Merigan, Katzenstein, and Kozal. Pet App. 41a. As a co-owner of the patents, Stanford retains all the rights of a patentholder, including the rights to "make, use, offer to sell, or sell the patented invention within the United States, or import the patented invention into the United States, without the consent of and without accounting to the other owners." 35 U.S.C. § 262.

Stanford's insistence that there is a "cloud" on its title or that its rights are "uncertain" or "extinguish[ed]" (Pet. 12, 15-16, 18) is thus off-point, as are

the hyperbolic claims of its *amici*.[1] Leaving aside that the district court held the patents invalid as obvious (563 F. Supp. 2d 1016 (N.D. Cal. 2008)), Roche still could not sue Stanford for infringement. Stanford may freely practice the invention in conducting further research. If Stanford is concerned that Roche will not make the invention sufficiently available to the public, Stanford can license it; it can even license it for a pittance, or for free, "without accounting" to Roche. 35 U.S.C. § 262.

Stanford's real objection, which only occasionally surfaces in its petition, seems to be that it is not the *exclusive* owner of the patent. Pet. 3 (bemoaning that Stanford's ownership is "shared"). Stanford apparently wishes to exclude from the marketplace anyone who does not agree to pay Stanford a hefty royalty. Stanford's desire for private monetary gain has nothing to do with clarity of title or bringing valuable scientific discoveries to the public. On the contrary, Stanford's effort to exclude Roche from practicing the patented invention would *reduce* opportunities for the public to benefit from the invention, which was conceived at Cetus's laboratory using Cetus's own research materials and expertise. The Court should not be misled: Stanford's petition does not seek clarification of Stanford's right to commercialize the invention — a right Stanford already possesses — but rather to *restrain* competition by other parties who will not play by Stanford's rules.[2]

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[1] *See, e.g.*, Wis. Alumni Research Found. *Amicus* Br. 16 (suggesting that an inventor could "leav[e] the research institution with no title")

[2] This case does not present the hypothetical scenario in which all inventors have assigned their rights to a non-funded entity. The sophistication of large universities and technology

Stanford offers no reason to think that the Bayh-Dole Act was designed to favor exclusive commercialization by private universities rather than shared commercialization with private industry. As Stanford and its *amici* rehearse at length, the Act was designed to remedy an inefficient system under which the *government* hoarded inventions in ways that made it difficult for the private sector (including universities *and* industry) to use them without navigating labyrinthine bureaucracy. *See, e.g.*, Pet. 8; Ass'n of Am. Univs. *Amicus* Br. 16-17. Nothing in this case raises that concern. Stanford may use the patent as it wishes; the only thing it cannot do is exclude its co-owners, a characteristic of the patent law that has been in place for decades. *See, e.g.*, *Talbot* v. *Quaker-State Oil Refining Co.*, 104 F.2d 967, 968 (3d Cir. 1939) (co-owner may use invention without consent of co-owners or sharing of profits, even though that "unlimited right" "may, for all practical purposes, destroy the monopoly and so amount to an appropriation of the whole value of the patent").

B. This Case Presents No Issue Of Government Patent Rights

Stanford urges that the Federal Circuit's "reasoning" would "permit" an inventor "to terminate the government's rights." Pet. 20; *see also* Pet. 15 ("the Federal Circuit's holding means that the federal government has no rights unless the inventor consents"); Wis. Alumni Research Found. *Amicus* Br. 16. Again, that concern is hypothetical at best.

One searches the Federal Circuit's opinion in vain for any "reasoning" directed to government rights.

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companies engaged in innovative discovery makes it highly unlikely that such a situation would ever arise.

The Federal Circuit was not asked to decide, and did not decide, what would happen if the government exercised its statutory option to take title to an invention subject to a prior assignment by an inventor. On the contrary, it expressly reserved the possibility that the Bayh-Dole Act might give the government "a discretionary option to [the inventor's] rights." Pet. App. 19a. It also did not rule out the possibility that the government might have remedies against Stanford or that Stanford might have remedies against Dr. Holodniy. Pet. App. 20a n.1.

Accordingly, the Court should not presume that this case will implicate any important federal interest. In the event a future case creates uncertainty as to the federal government's rights, the government will doubtless make its views heard as a party.

C. Stanford's Objection Is Splitless, Fact-Bound, And Highly Unusual

Stanford's petition does not present any of the traditional indicia that would merit this Court's attention. Unlike many cases involving patents, this case arises under the Bayh-Dole Act, over which the Federal Circuit concededly does not have exclusive jurisdiction. Pet. 19. Further percolation is thus not only possible but likely. Indeed, the Federal Circuit cited two other decisions raising issues similar to the one below. Pet. App. 20a-21a (citing *Univ. of Pittsburgh* v. *Townsend*, 2007 U.S. Dist. LEXIS 56860 (E.D. Tenn. Aug. 3, 2007), *aff'd*, 542 F.3d 513 (6th Cir. 2008), and *Fenn* v. *Yale Univ.*, 393 F. Supp. 2d 133, 141-42 (D. Conn. 2004)). Stanford does not even

discuss them, even though they demonstrate that there is no conflict among lower courts.[3]

In addition to being splitless, the decision below is highly fact-dependent, turning as it does on the particular language that Stanford and Cetus used in their respective agreements. As Stanford admits, universities can easily avoid the ruling below by "choos[ing] to revise their contracts with researchers and inventors" to grant immediate assignments, rather than simply "agree[ing] to assign" their inventions in the future. Pet. 17.

Although Stanford asserts that universities have used "agree to assign" language in their form agreements for 30 years (Pet. 18), it cites nothing to support that claim. Not one of Stanford's many *amici* states that it has used such language. On the contrary, publicly-available form agreements of at least one of the *amici* reveal that they require employees to enter into immediate assignments, not mere agreements to assign. *See, e.g.*, Massachusetts Institute of Technology, Inventions and Proprietary Information Agreement, *available at* http://web.mit.edu/tlo/www/misc/forms.html#TECHNOLOGY (requiring all M.I.T. employees to agree that "I will disclose promptly to and assign to, *and I hereby assign* to, M.I.T., all rights to all inventions") (emphasis added). Notably, Stanford previously boasted that its policies *differed* from those of "industry and many other universities" in that Stanford "allows all rights to remain with the inventor if

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[3] One of Stanford's *amici* takes pains to distinguish the cases (Wis. Alumni Research Found. *Amicus* Br. 8 n.2), a counterproductive effort that, if successful, would prove only that this issue is so rare that it has arisen in exactly one case—this one—in the 30 years since the Bayh-Dole Act became law.

possible." Pet. App. 13a (quoting Stanford's Administrative Guide to "Inventions, Patents, and Licensing"); *see also* Pet. App. 19a.

Moreover, the Federal Circuit's interpretation of agreements to assign has been settled for nearly two decades. *See* Pet. App. 13a (citing, *e.g.*, *Arachnid, Inc. v. Merit Indus., Inc.*, 939 F.2d 1574, 1580-81 (Fed. Cir. 1991)). To the extent any universities continued to use mere agreements to assign, they did so at their peril and presumably for their own reasons.[4]

In addition to turning on specific contractual language, this case also arises in the unusual context in which a foundational invention was conceived not at a university receiving federal funds, but at a small company that did not receive federal funding (Cetus), and was only later incorporated into a federally funded project at a large university (Stanford). In the typical Bayh-Dole case, the groundbreaking research is all done at the same grantee institution and subsequently provided to a company for product development and marketing. The Court should view with skepticism Stanford's claims about the frequency with which the facts of this case will recur.[5]

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[4] Stanford itself has articulated its policy of seeking to have inventors keep ownership of their own inventions "if possible." Pet. App. 13a. There may be many reasons for such a policy, including creating incentives for top researchers to join a university's faculty.

[5] The fact that a decision "of first impression" generated "a flurry of commentary and concern" (Pet. 19) does not suggest that the issue is important or will come up often. Sophisticated academic institutions like Stanford and its *amici* frequently produce "flurr[ies] of commentary," especially when they lose a case. And the only piece of "commentary" Stanford cites was co authored by counsel for one of Stanford's *amici*. Pet. 19 n.1

D. The Question Presented Will Not Be Outcome-Determinative

A further reason for this Court to deny review is that it is highly unlikely that this issue will have any impact even in *this* case. As pointed out above, a ruling that Dr. Holodniy's assignment did not "terminate" Stanford's patent rights would change nothing, as Stanford is already a co-owner of the patent. Moreover, Stanford's effort to hold Roche liable for infringing a patent is likely to fail on other independent grounds, notably that the district court has already held the patent invalid for obviousness. Pet. App. 2a (citing 563 F. Supp. 2d 1016 (N.D. Cal. 2008)). Roche also contended below that it can practice the patent due to the licenses Cetus received from Stanford and Dr. Merigan in 1988 and 1989. The Federal Circuit has not yet reached these issues, but each provides an independent ground to end the case in Roche's favor.

Accordingly, were this Court to grant review, there is every likelihood that its decision would not affect the outcome in this or any other case. If this ruling were truly the momentous sea change Stanford says it is, a case that actually turns on the issue should not be far behind.

(citing article co-written by Howard W. Bremer, emeritus patent counsel for Wisconsin Alumni Research Foundation); *see also* Wis. Alumni Research Found. *Amicus* Br. 9 n.3, 10 n.5, 12 n.7 (citing additional articles by Mr. Bremer written prior to the Federal Circuit's decision).

II. THE FEDERAL CIRCUIT'S DECISION IS CORRECT

Although the considerations discussed above are ample reason to deny review, Stanford's petition additionally lacks merit.

A. The Bayh-Dole Act Does Not Alter A Co-Inventor's Right To Assign His Shared Interests In An Invention

Inventors own their intellectual property unless and until it is assigned to another by an instrument in writing. *Crown Die & Tool Co.* v. *Nye Tool & Machine Works*, 261 U.S. 24, 35-37 (1923). The patent law gives an inventor an express statutory right to assign his interest in patents and patent applications. 35 U.S.C. § 261 ("Applications for patent, patents, or any interest therein, shall be assignable in law by an instrument in writing."). An assignment may occur between an invention's conception and the issuance of a patent, in which case legal title to the ensuing patent will pass to the assignee upon grant of the patent. *Gayler* v. *Wilder*, 51 U.S. (10 How.) 477, 493 (1850). An inventor may also assign expectant interests in a future invention not yet in being, in which case the creation of the invention automatically transfers the inventor's rights in it to the assignee, without need of any further action. *FilmTec Corp.* v. *Allied-Signal Inc.*, 939 F.2d 1568, 1572-73 & n.8 (Fed. Cir. 1991) (citing Williston, *Transfers of After-Acquired Personal Property*, 19 Harv. L. Rev. 557 (1906)).

The Bayh-Dole Act did not amend or alter these longstanding principles. Where, as here, the government has not exercised its discretionary right to take title, "title remains with the named inventors

or their assignees. Nothing in the [Bayh-Dole] statute, regulations, or . . . caselaw indicates that title is automatically forfeited." *Cent. Admixture Pharmacy Servs., Inc.* v. *Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347, 1352-53 (Fed. Cir. 2007).

Stanford contends that the Act provides that ownership "vests with the university so long as it makes an ownership election within a reasonable period of time." Pet. 10. The Act says nothing of the kind. Rather, the Act sets forth steps that a federally-funded institution must take in order to "*retain* title" as against the government. 35 U.S.C. § 202(a) (emphasis added). The Act therefore presumes that the funded institution that would otherwise *have* title (but for governmental interests) may elect to "retain" it. Here, as the court of appeals recognized, Stanford retained the title it would otherwise have had: the title acquired from the co-inventors other than Dr. Holodniy. *See* Pet. App. 19a. But nothing in the Act forbids Dr. Holodniy's assignee from sharing in title, nor does the Act permit Stanford to sue the assignee for infringement. As courts have recognized, "the primary purpose of the Bayh-Dole Act is to regulate relationships of small business and nonprofit grantees with the Government, not between grantees and the inventors who work for them." *Fenn* v. *Yale Univ.*, 393 F. Supp. 2d 133, 141-42 (D. Conn. 2004); *see also Therien* v. *Trs. of Univ. of Pa.*, 2006 WL 83448, at *3 (E.D. Pa. Jan. 10, 2006).

Stanford cites several provisions that delineate the respective rights and obligations between institutions or companies that *receive* federal funds on the one hand and the federal government itself on the other. Pet. 9. Those provisions remain applicable as between Stanford and the government, and nothing

in Dr. Holodniy's assignment alters them. The court of appeals accordingly left open the possibility that Dr. Holodniy's assignment to Cetus might have violated his or Stanford's obligations under 35 U.S.C. § 202(c)(7) or that Stanford or the federal government might have other remedies under the Act. Pet. App. 20a n.1. However, nothing in the Act operates to abrogate the rights of Cetus (or its successor, Roche), which did not receive any federal funding for its groundbreaking research.

Stanford essentially reads the Bayh-Dole Act as giving it a confiscatory power over the intellectual property of entities with which it collaborates. Indeed, Stanford argues that it can even undo valid assignments *retroactively* by obtaining federal funds with respect to inventions *already conceived and assigned*. *See* Pet. 12 (arguing that the Act encompasses inventions that were "conceived earlier without using government funding" and only "*later* reduced to practice . . . using government funding" (emphasis added)). Stanford's position would allow it to promise a collaborating entity shared rights to any invention conceived during the collaboration, but then avoid its promise by subsequently obtaining federal funds.

Despite numerous requests, Stanford has never produced the actual funding agreement with the federal government that allegedly bears upon the inventions at issue in this case. Nor has Stanford demonstrated how Dr. Holodniy's work at Cetus or the contributions of Cetus and its scientists are connected to research grants awarded to Stanford. Having obtained the benefit of Dr. Holodniy's residence at a private company, Stanford's failure to produce the applicable funding agreement and prove

that the Cetus material, reagents, and expertise were subject to it suggests that Stanford is trying to whipsaw Cetus (now Roche) and take property rights away from the company.[6]

The goals of the Bayh-Dole Act are advanced by allowing Cetus/Roche to continue to produce the HIV test kits that have allowed physicians to use the PCR assay to quantify and treat HIV in hundreds of thousands of patients worldwide. It is that development work, not Stanford's desire to suppress it or obtain an undeserved windfall, that will "promote the commercialization and public availability of inventions made in the United States by United States industry and labor." 35 U.S.C. § 200. Nothing in the Bayh-Dole Act or its underlying policies supports allowing Stanford to use federal funding as an offensive weapon to avoid contractual obligations. *See Univ. of Pittsburgh* v. *Townsend*, 2007 U.S. Dist. LEXIS 56860, at *60-61 (E.D. Tenn. Aug. 3, 2007) (inventor's assignment to third party was unaffected by university's election to retain title under the Bayh-Dole Act where "the University's ostensible exercise of its right to title . . . occurred after Dr. Townsend's assignment"), *aff'd*, 542 F.3d 513 (6th Cir. 2008).

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[6] Stanford asserts that it "presented substantial evidence" that the patents-in-suit were conceived under federal grants. Pet. 12. Conspicuously absent is proof that Dr. Holodniy's work at Cetus and the information obtained from Cetus was subject to federal research grants. The district court held that the invention was "conceived" and the assay "completed" before Dr. Holodniy left Cetus (Pet. App. 56a); Stanford refused to provide any asserted date of conception (Pet. App. 58a n.7).

B. Stanford's Additional Objections Do Not Merit Review

In an effort to supplement its erroneous reading of the Bayh-Dole Act, Stanford raises three arguments that do not raise any substantial federal question and, at most, contend that the courts below made errors in factfinding or misapplied properly stated rules of law. Those arguments do not warrant review. *See* Supreme Court R. 10.

First, Stanford appears to quarrel with the court of appeals' interpretation of Dr. Holodniy's assignment agreement. Pet. 13-14 (arguing that the Federal Circuit should not have applied "its present assignment case law"). Stanford contends that Dr. Holodniy's Visitor Confidentiality Agreement should have been interpreted as conveying "an interest that was subject to his contract with Stanford." Pet. 14. But the court of appeals concluded that Dr. Holodniy's contract with Stanford was only an "agreement to assign" and, accordingly, had no effect on the present assignment to Cetus. Pet. App. 13a. Stanford's dissatisfaction with that interpretation is not a substantial issue of federal law. Rather, the Federal Circuit simply applied its established rulings regarding the effect of assignments of patent rights. *Id.* Indeed, Stanford offers no developed argument suggesting that the Federal Circuit's interpretation of the agreements was even incorrect. Pet. 13-14.

Second, Stanford objects to the fact that "a single inventor could alienate his rights for a fee, usurping the rights of co-inventors to share in any financial benefits from commercializing the intellectual property." Pet. 14. That principle flows not from the Federal Circuit's decision in this case, but from the patent law itself, which provides that a patent owner

may "make, use, offer to sell, or sell the patented invention . . . *without the consent of and without accounting to the other owners*." 35 U.S.C. § 262 (emphasis added); *see also Talbot*, 104 F.2d at 968. This Court does not sit to revise Congress's statutory enactments, even if Stanford believes them to be unwise.

Third, Stanford complains that it lacked "actual knowledge" of Dr. Holodniy's agreement. Pet. 16. That is simply incorrect. Stanford does not dispute that Dr. Holodniy was acting as Stanford's agent when he signed the VCA with Cetus. His work at Cetus "related directly to his infectious disease research" at Stanford, and indeed it was his supervisor at Stanford, Dr. Merigan, who "directed" Dr. Holodniy to spend nine months working at Cetus for that purpose. Pet. App. 16a-17a. Stanford's complaint appears to be that it should not have been "presumed to know" of Dr. Holodniy's assignment to Cetus. Pet. 16. But just as the opinion below did not invent 35 U.S.C. § 262, it also did not invent the doctrine that "a principal is charged with the knowledge of the agent acquired by the agent in the course of the principal's business." *Curtis, Collins & Holbrook Co.* v. *United States*, 262 U.S. 215, 222 (1923); *see also Santillan* v. *Roman Catholic Bishop of Fresno*, 163 Cal. App. 4th 4, 11 (2008) ("For this purpose, there is no difference between constructive and actual notice. The rule applies to employees, who are agents of their employers.") (citation omitted); 3 Witkin, Summary of California Law, Agency § 150 (2005) ("[A] corporation may be charged with notice of matters known to its employees."); Restatement (Third) of Agency § 5.04 cmt. b (2006) ("Ordinarily, an agent's failure to disclose a material fact to a principal does not defeat imputation.").

This Court is not the proper forum for Stanford's contention that it should be exempt from the common-law imputation of its agent's knowledge. Pet. 16. Stanford is free to approach the California Legislature with its view that "it would be far more efficient, and would better serve the public interest, to impose some or all of this burden on the for-profit company." Pet. 17. Suffice it to say, however, that Stanford has not shown that the court below erred in not requiring private research laboratories like Cetus to investigate and police the obligations of employees of a large university that has a sophisticated technology transfer office.

Stanford and its agents should be bound by the agreements that they sign. Stanford's claim that it was treated unfairly rings particularly hollow given that Stanford *itself* sought out the collaboration, that it never told Cetus that Stanford would try to take for itself the results of Dr. Holodniy's onsite work at Cetus and his unfettered access to Cetus expertise and equipment, and that it seeks not to protect its own unchallenged right to use the invention, but to prevent Cetus (and Roche) from doing the same.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted,

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REPLY BRIEF

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In The
Supreme Court of the United States

BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY,
Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC.,
ROCHE DIAGNOSTICS CORPORATION,
ROCHE DIAGNOSTICS OPERATIONS, INC.,
Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITIONER'S REPLY BRIEF

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INTRODUCTION

The Brief in Opposition ignores the statutory language, structure, and historical background of the Bayh-Dole Act. As Roche acknowledges, the fundamental premise of the Federal Circuit's holding, and of Roche's position, is that "the Bayh-Dole Act nowhere alters an inventor's basic freedom to assign his own rights in [a federally funded] invention to a third party." Opp. Br. 2. Yet Roche fails to even mention section 202(d), the Bayh-Dole provision specifically limiting how inventors may obtain rights in federally funded inventions. Nor does Roche rebut the showing by Stanford and over 60 amici that Congress intended Bayh-Dole to provide a clear, statutory right to title in federally funded inventions to university contractors. Statutory rights to federally funded inventions do not depend on assignment language in employment contracts or invention agreements. The only rights implicated by such agreements are ones that exist ***after*** the application of the Act.

Before Bayh-Dole, the government, not individual inventors, held title to federally funded inventions. Because the government underutilized these inventions for decades, the Act reallocated the primary right to title to universities. Neither Roche nor the Federal Circuit identified any support in the statute or legislative history for the notion that Congress intended to allow individual inventors to assign rights in federally funded inventions outside this statutory structure.

Although Roche argues that this case is unique, the Federal Circuit's decision reaches far beyond

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Stanford's dispute with Roche. As the extensive amicus briefing has shown, the issues presented here have widespread and profound implications for billions of dollars provided annually for government-sponsored research throughout the nation.

This Court's review is urgently needed. Because of the Federal Circuit's exclusive jurisdiction over patent appeals, other circuits will not likely consider the issue. Moreover, the Federal Circuit's decision casts immediate doubt on research institutions' title under Bayh-Dole for past and new inventions arising from federally funded research. As history demonstrates, without clarity of title, those inventions will go undeveloped, and the principal purpose of the Bayh-Dole framework will be frustrated.

I. ROCHE OFFERS VIRTUALLY NO DEFENSE ON THE MERITS OF THE FEDERAL CIRCUIT'S CONSTRUCTION OF THE BAYH-DOLE ACT.

Roche's Brief rests on the faulty premises that (1) individual inventors own patent rights in federally funded inventions independent of the Bayh-Dole Act, (2) they have the right to assign such inventions to third parties outside the statutory scheme, and (3) that third parties are free to receive such assignments, regardless of the Act or whether the university or federal government agrees.

Strikingly, while repeatedly claiming that Bayh-Dole addresses only the rights of the government and universities and not inventors' rights, Roche never addresses section 202(d), which specifically limits how

inventors may obtain rights in federally funded inventions:

> If a contractor does not elect to retain title to a subject invention in cases subject to this section, the Federal agency may consider and after consultation with the contractor grant requests for retention of rights by the inventor subject to the provisions of this Act and regulations promulgated hereunder.

35 U.S.C. § 202(d). Retention of patent rights by an inventor—and thus the ability to assign them away—is strictly controlled, and is neither presumed nor automatic. And section 202(d)'s requirements were indisputably not met in this case.

Moreover, Roche's position rests on the mistaken assumption that before Bayh-Dole was enacted, an inventor had the same patent rights in a federally funded invention as in other inventions. That is not true. As detailed by the amici, before Bayh-Dole, the federal government—not individual inventors—held all such invention rights. Br. of Ass'n of Am. Univs. et al. as Amici Curiae in Support of Petitioner 11-15 (citing, *e.g.*, 42 U.S.C. § 5908(a) (1976)). Bayh-Dole altered the statutory scheme to give universities the right to retain title. 35 U.S.C. § 202(a). The Act did not grant default invention rights in federally funded inventions to individual inventors.

Roche also misapprehends the Federal Circuit's decision in *Central Admixture Pharmacy Services, Inc. v. Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347 (Fed. Cir. 2007). If *Central Admixture* establishes anything, it is that Bayh-Dole governs inventors' rights

in federally funded inventions: after the university waived its statutory right to the invention, the inventor applied for the rights as required under Bayh-Dole, and the federal agency approved the application. *Id.* at 1351. The case *applied* the Act, and did not hold that the inventor had rights independent of Bayh-Dole.

II. THIS COURT'S REVIEW IS URGENTLY NEEDED.

A. Roche Cannot Minimize the Importance of the Federal Circuit's Decision.

Roche's contention that this case is "highly unusual" (Opp. Br. 14-16) is contradicted by the grave concerns detailed by more than 60 university and university association amici. The Federal Circuit's opinion creates an immediate and widespread harm to universities and other research institutions that receive federal funding for research. Clarity of title is essential to achieving the goals of the Bayh-Dole Act. Absent that clarity, companies will be unwilling to pay to license federally funded inventions, and universities will be unable to commercialize those inventions. This was the state of affairs before Bayh-Dole.

1. Roche focuses on irrelevant details while ignoring the broad implications of the Federal Circuit's decision.

Roche contends that this case does not present the question of whether an inventor can unilaterally terminate a university's rights under Bayh-Dole because Stanford still possesses rights from Dr. Holodniy's co-inventors. Opp. Br. 11-13. Roche further argues that shared ownership of the invention is

appropriate here because of Cetus's purported contribution to the invention. *Id.* 12-13, 24. Both arguments are red herrings.

As Roche recognizes, the premise of the Federal Circuit's decision is that "the Bayh-Dole Act nowhere alters an inventor's basic freedom to assign his own rights in [a federally funded] invention to a third party." Opp. Br. 2. It directly follows that, if Holodniy were the sole inventor, he could have assigned the entirety of the rights to a third party, thus wholly depriving Stanford (and the federal government) of any rights in the invention. Moreover, under the Federal Circuit's analysis, Holodniy could have assigned rights to a third party that had no prior contact with Dr. Holodniy or knowledge of the invention. Thus, Cetus's alleged involvement and Stanford's ownership of the co-inventors' rights are pure happenstance unrelated to the logic or reach of the Federal Circuit's holding.[1]

2. A research institution's rights flow from the statutory framework of the Bayh-Dole Act, not contractual assignment language.

A research institution's right to elect to retain title under the Bayh-Dole Act does not turn on whether an inventor has made an assignment to the research institution. The Act itself gives Stanford the right to elect to retain title in the federally funded invention, and has specific requirements that must be met for an inventor to obtain title. 35 U.S.C. § 202(a)-(b), (d). By making title to federally funded inventions depend on

[1] Indeed, the Federal Circuit's decision would allow inventors to assign rights to themselves, in violation of Section 202(d).

the ad hoc assignments of title by individual inventors, the Federal Circuit has introduced a lack of clarity that is anathema to the statutory scheme.

This very case is a troubling example of the pitfalls of making Bayh-Dole dependent on inventor assignments. Stanford's employment agreement with Dr. Holodniy expressly gave Stanford the right to government-funded inventions, to secure compliance with the Bayh-Dole framework. App. 118a-119a. Despite this right, the Federal Circuit gave priority to the later executed VCA's "present assignment" provision, App. 12a-15a, while giving no effect to the prior-existing agreement with Stanford. *Id.* The court provided no explanation why a later present assignment should terminate a prior contractual commitment, and there is none.

Contrary to Roche's assertion (Opp. Br. 22), the Federal Circuit's lack of deference to the Bayh-Dole statutory framework over a new application of its present assignment law is unprecedented. The Federal Circuit never previously concluded that a present assignment clause terminates prior contractual obligations, much less obligations directed to Bayh-Dole compliance. Whether through the allocation of inventorship rights under Bayh-Dole or his prior agreement with Stanford, Dr. Holodniy had no invention rights in any government-funded inventions to give to Cetus, whether through present assignment or otherwise.

3. The problems created by the Federal Circuit's decision cannot be avoided by using different contractual assignment language.

Roche suggests that Stanford is uniquely harmed by the Federal Circuit's decision because few universities use the "agree to assign" language used in Stanford's agreement. Opp. Br. 15-16. Roche's suggestion is meritless. Many universities have inventors' agreements using similar language. *See, e.g.*, Univ. of Cal., State Oath of Allegiance, Patent Policy, and Patent Acknowledgement, available at http://www.ucop.edu/ott/genresources/patentac.html; Univ. of Wis. Sys., Patent Policy (G34), available at http://www.uwsa.edu/fadmin/gapp/gapp34.htm#appndx1.

Ensuring clarity of title is hardly the simple matter of changing a few words as Roche would have the Court believe. Contrary to Roche's contention, universities cannot "easily" change their agreements to avoid the Federal Circuit's decision. Opp. Br. 15. Further, changing future contracts does nothing to remedy the confusion created by the Federal Circuit's decision as to the many years of already ongoing or comp eted research. Nor do prospective changes remedy problems caused by assignment agreements into which inventors may have entered with third parties prior to making an assignment to a university.

It would wholly frustrate the purpose of Bayh-Dole to have a university's ownership of a federally funded invention turn on a battle of contractual assignment clauses. This is particularly true in the context of

academic research, where the existence, dates, and terms of any competing assignment by the individual researcher cannot be known with certainty.

B. The Federal Circuit's Decision Deprives the Government of Rights Granted by the Bayh-Dole Act.

Roche's contention that the Federal Circuit's opinion will not affect government rights (Opp. Br. 13-14) ignores the opinion's necessary implications and Roche's own sweeping arguments about inventors' rights outside the statutory scheme.

Most immediately, the decision eliminates the government's statutory right to control whether an individual inventor will have rights in a federally funded invention. Under the Act, inventors have rights in federally funded inventions ***only*** if the federal government consents after consultation with the research institution. 35 U.S.C. § 202(d). This is the only means through which Holodniy could have obtained the rights purportedly transferred to Roche in this case. It is the federal government that succeeds to the rights of the research institution if the research institution fails to comply with the Act's disclosure and election requirements. *See* 35 U.S.C. § 202(c)(1).

Although there was no such consent in this case, the Federal Circuit nonetheless gave Dr. Holodniy exclusive rights to his federally funded work, which the Federal Circuit then held were transferred to Cetus. The Federal Circuit's decision in effect creates a new category of statutory rights of individual inventors in federally funded inventions that exist

independent of the statutory scheme and do not require governmental consent under Section 202(d).

Roche next argues that the Federal Circuit "did not rule out the possibility" that the government might have other remedies.[2] No such remedies would be necessary if compliance with the Bayh-Dole Act is required.

Roche finally submits that this Court should not "presume that this case will implicate any important federal interest." Opp. Br. 14. If there is any doubt, Stanford suggests it would be appropriate for this Court to call for the views of the Solicitor General.

C. The Court Should Not Await a Circuit Conflict.

The lack of a Circuit split does not counsel against review in this case. The Federal Circuit has pronounced a broad rule of law applicable to federally funded programs throughout the country, and declined to rehear the issue *en banc*. Although the issue could theoretically arise in another Circuit, as a practical matter the issue is most likely to arise in the Federal Circuit, which has exclusive jurisdiction over patent appeals. *See* 28 U.S.C. § 1295(a)(1). Because the harm

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[2] Roche's suggestion that the government may have remedies against a university is contrary to the Act's purpose to further research and foster commercialization of federally funded inventions. Its further suggestion that a university should sue the inventor is illusory: the idea that an individual inventor could make the university whole has no basis in reality.

from the Federal Circuit's decision is real and immediate, the question should be heard now.[3]

III. ROCHE'S APPEAL TO EQUITIES IS MISPLACED AND UNSUPPORTED BY THE FACTS.

Roche's statement of the facts relies heavily on innuendo, suggesting that the Court should deny certiorari because the equities somehow favor Roche. The equities alleged by Roche are not only irrelevant, but also contradict the factual record.

Initially, as shown above, the broad rule announced by the Federal Circuit does not depend on the particular facts here. Under that rule, an individual inventor is free to assign rights in a federally funded invention regardless of either the level of contributions by third parties, or whether the university retains some rights through other co-inventors. Indeed, the Federal Circuit's reasoning compels the same result had a single inventor assigned all rights in a federally funded invention to a holding company that did nothing more than purchase and license patents.

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[3] Roche also argues that even if Stanford has standing, Roche would still have other defenses, including the purported invalidity of the patent. Opp. Br. 17. That Roche could later prevail on other grounds is no reason for the Court to decline review of the important legal question presented. The Court often grants review to resolve important legal questions, even where the petitioner may ultimately lose on other legal or factual grounds. In any event, Stanford has a strong position on the merits, including patent validity issues that were briefed to, but not reached by, the Federal Circuit.

In any event, Roche paints a misleading and dramatically skewed picture of this case. For example, Roche ignores that its claim to patent ownership rests on Dr. Holodniy signing a Visitor's Confidentiality Agreement ("VCA") in which the intellectual property clause was buried. Roche also brushes past the fact that this VCA was signed 15 years before Roche asserted any ownership rights. Stanford and Roche negotiated for years in an attempt to reach an acceptable license arrangement. Far from seeking to prevent Roche from commercializing the technology, Stanford simply seeks fair compensation for Roche's longstanding, unlicensed use of Stanford's patented technology.[4]

Roche also ignores that Cetus made no contribution to the clinical work that resulted in Stanford's inventions. Roche argues that Dr. Holodniy performed laboratory work on an assay at Cetus, Opp. Br. 3-4, but does not dispute that the clinical work was performed exclusively at Stanford without Cetus's input. *See* App. 39a-40a ("Cetus was not involved in these experiments."). Nor does Roche dispute that Holodniy's assay work at Cetus was published in abstracts months before the Stanford clinical research began. App. 37a. Holodniy—just like the rest of the HIV research community—was entitled to rely freely on this publicly available information. Moreover, the assay Roche attempts to equate with the claimed inventions was described in a published scientific article that the Patent Office considered before

[4] Thus, Roche's argument regarding exclusive commercialization (Opp. Br. 13) is inapposite. Further, the Act gives research institutions—not private concerns—the right to retain title, and resulting royalties benefit the public by funding further research. 35 U.S.C. § 202(a), (c)(7)(C).

granting Stanford's patent. Roche's attempts to conflate the publicly disclosed assay with Stanford's inventions should be rejected.

Finally, Roche's claim that Stanford "secretly" patented the claimed inventions is baseless. Opp. Br. 6-7. Dr. Holodniy disclosed the prior assay work to Cetus, but Cetus declined to pursue any patents based on that assay, and the assay work was thereafter published. App. 37a-38a. Further, after performing the later clinical work resulting in the inventions, Stanford published the results and methodology widely. App. 40a. Cetus personnel learned of this clinical work shortly thereafter, but never made any claim to ownership or contribution. *Id.* Indeed, both courts below held that because Roche knew of Stanford's claims to sole title over the clinical invention for many years before this suit, Roche is time-barred from pursuing any affirmative ownership claim. App. 22a-27a, 45a-51a.

IV. ROCHE IGNORES THE ENORMOUS ONE-SIDED BURDEN OF DISRUPTING THE PATH TO CLEAR TITLE UNDER THE BAYH-DOLE ACT.

Roche also avoids the Federal Circuit's failure to take into account relative burdens in establishing its new rule, contending that it is an issue of agency law for state legislatures. Opp. Br. 24. But this misses the point. Whether Stanford had actual or constructive knowledge of the VCA is a hotly contested issue,[5] but

[5] Roche's assertion (without citation) that Stanford does not dispute that Dr. Holodniy acted as Stanford's agent in signing the VCA (Opp. Br. 23), is false. *See, e.g.*, App. 16a-18a.

it was undisputed that Cetus had actual knowledge of Holodniy's status as a Stanford employee and the Bayh-Dole Act. Yet the Federal Circuit placed the entire burden on Stanford (and any prospective licensee of the university) to make sure that Holodniy did not purposely or inadvertently give away rights to Bayh-Dole inventions. The Federal Circuit's holding would require universities to so heavily police their researchers as to require an enormous administrative load, or to wholly preclude beneficial collaborations between researchers and third parties. Ultimately, the Federal Circuit's opinion turns on its head one of the Bayh-Dole Act's principal objectives—establishing a uniform and clear path for establishing title to inventions arising from federally funded research at universities.

CONCLUSION

The petition should be granted.

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AMICUS CURIAE BRIEF

No. 09-1159

In the Supreme Court of the United States

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, PETITIONER

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

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QUESTION PRESENTED

The University and Small Business Patent Procedures Act of 1980, 35 U.S.C. 200 *et seq.*, commonly known as the Bayh-Dole Act, establishes a framework for determining ownership interests in federally funded inventions. Under the Act, college and university, nonprofit, and small business federal contractors may "elect to retain title" to any invention conceived or reduced to practice in the performance of federally funded research. 35 U.S.C. 202(a). "If [the] contractor does not elect to retain title" to such an invention, the federal government may grant the inventor rights in the invention. 35 U.S.C. 202(d). The question presented is as follows:

Whether an inventor who is employed by a contractor that elects to retain rights in an invention may defeat the contractor's right to retain title under the Bayh-Dole Act by contractually assigning his putative rights in the invention to a third party.

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In the Supreme Court of the United States

No. 09-1159

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, PETITIONER

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

This brief is submitted in response to this Court's invitation to the Solicitor General to express the views of the United States. In the view of the United States, the petition for a writ of certiorari should be granted.

STATEMENT

1. The United States has long supported technological research and innovation through funding grants to colleges and universities, nonprofit organizations, and small businesses. That support is substantial: more than half of the scientific and technical research conducted at colleges and universities in the United States is funded by federal grants. See Gov't Accountability Office, GAO-09-742, *Information on the Government's Right to Assert Ownership Control Over Federally Funded Inventions* 1 (2009) (*GAO Report*).

Since 1980, the ownership of inventions arising out of federally funded research has been governed by the University and Small Business Patent Procedures Act of 1980, 35 U.S.C. 200 *et seq.*, commonly known as the Bayh-Dole Act. Because the balance of interests struck in the Act is best understood in light of the history of ownership of federally funded inventions, this brief first describes that history and then describes the specific provisions of the Act at issue here.

2. Before 1980, no uniform source of law governed ownership of inventions that resulted from federally funded research. Instead, a "melange of 26 different agency policies" governed title to such inventions. H.R. Rep. No. 1307, 96th Cong., 2d Sess. Pt. 1, at 3 (1980) (*House Report*). For some agencies, statutes provided that title to patents on such inventions automatically vested in the federal government unless the agency waived its rights. See, *e.g.*, 42 U.S.C. 2182, 5908(a) (1976) (Department of Energy); 42 U.S.C. 2457(a) (1976) (National Aeronautics and Space Administration). Those vesting statutes superseded an inventor's common law rights in his invention and his statutory patent rights. See *Arachnid, Inc.* v. *Merit Indus., Inc.*, 939 F.2d 1574, 1578 (Fed. Cir. 1991) (describing inventor's common law and statutory rights). An inventor working on a federally funded project subject to those statutes therefore was not free to assign rights in his invention to third parties. Such an inventor had "no right to assign" because title to his invention "automatically vested in the United States" by "operation of law." *FilmTec Corp.* v. *Hydranautics*, 982 F.2d 1546, 1550, 1553 (Fed. Cir. 1992), cert. denied, 510 U.S. 824 (1993).

In contrast to agencies operating under vesting statutes, other agencies addressed ownership of patents for federally funded inventions by entering into agreements

with individual research institutions. The National Science Foundation (NSF) and the Department of Health, Education and Welfare (HEW), for example, operated under Institutional Patent Agreement (IPA) programs adopted in the 1960s and 1970s. See David C. Mowery et al., *Ivory Tower and Industrial Innovation: University-Industry Technology Transfer Before and After the Bayh-Dole Act* 45 (2004). IPAs gave universities with established technology-transfer programs a first option to own federally funded inventions. See S. Rep. No. 480, 96th Cong., 1st Sess. 21 (1979). The university's right was subject to a number of conditions, including a requirement to report the invention to the government, grant the government a royalty-free license, refrain from charging excessive royalties to other licensees, use royalty income for the support of education or research, refrain from assigning rights except in limited circumstances, and take effective steps to commercialize the inventions. See, *e.g.*, Federal Council for Science and Technology, *Report on Government Patent Policy* 330-339 (HEW IPA), 340-353 (NSF IPA) (1976) (*Patent Policy Report*).

Both the vesting statutes and the IPA programs had their shortcomings. Under the vesting statutes, the government often lacked the resources to develop and commercialize patent rights obtained through federally funded research. *GAO Report* 2; *House Report* 1-2. As a result, only about five percent of federally funded inventions were being marketed commercially. See 126 Cong. Rec. 8739 (1980) (statement of Sen. Dole); *GAO Report* 2. IPAs had a different but equally significant deficiency. The statutes governing several agencies, such as the NSF, prohibited the agencies from entering into contracts "inconsistent with any provision of law affecting the issuance or use of patents." 42 U.S.C. 1871(a) (1976). As a result, IPAs could not

allocate ownership rights in federally funded inventions by their own force; such allocations were possible only if the university obtained an assignment of rights from the researcher. See *Patent Policy Report* 330 (HEW IPA), 342 (NSF IPA). An institution's failure to obtain an effective assignment of rights from the researcher thus could compromise the allocation of rights and obligations under the IPA. See, *e.g.*, *Government Patent Policy Act of 1980: Hearing on H.R. 5715 Before the Subcomm. on Science, Research, and Technology of the H. Comm. on Science and Technology*, 96th Cong., 2d Sess. 80 (1980).

3. To address those shortcomings, Congress enacted the Bayh-Dole Act in 1980. The Act establishes a uniform framework for the disposition of rights in federally funded inventions. That framework was designed to "use the patent system to promote the utilization of inventions arising from federally supported research or development," while "ensur[ing] that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions." 35 U.S.C. 200. Congress sought to balance the interests of the contracting institution, the government, and the inventor in a manner that would best "promote collaboration between commercial concerns and nonprofit organizations, including universities," and that would encourage "future research and discovery." *Ibid.*

The Act prescribes title to certain federally funded inventions, which are called "subject invention[s]." A "subject invention" is "any invention * * * conceived or first actually reduced to practice in the performance of work under a funding agreement" between a contractor and a federal agency. 35 U.S.C. 201(e). A "contractor" is a "person, small business firm, or nonprofit organization that is a

party to a funding agreement." 35 U.S.C. 201(c). The term "funding agreement" is broadly defined as "any contract, grant, or cooperative agreement entered into between any Federal agency, other than the Tennessee Valley Authority, and any contractor for the performance of experimental, developmental, or research work funded in whole or in part by the Federal Government." 35 U.S.C. 201(b).

The Act creates a presumption that title to federally funded inventions will vest in the contractor, rather than in the government or inventor. The section of the Act titled "Disposition of rights" provides that a contractor may "elect to retain title to any subject invention." 35 U.S.C. 202(a). To do so, the contractor must "disclose each subject invention to the Federal agency within a reasonable time after it becomes known to contractor personnel responsible for the administration of patent matters." 35 U.S.C. 202(c)(1). The government "may receive title to any subject invention not disclosed to it within such time." *Ibid.*

The contractor's title in a federally funded invention, however, is subject to certain conditions. In addition to a requirement that the contractor report subject inventions to the federal agency, see 35 U.S.C. 202(c)(1), the Act requires the contractor to "make a written election within two years after disclosure to the Federal agency (or such additional time as may be approved by the Federal agency)" specifying whether it will retain title to the invention, 35 U.S.C. 202(c)(2). If the contractor is a nonprofit organization, it must "share royalties with the inventor," 35 U.S.C. 202(c)(7)(B), and must utilize the royalties or income remaining to further "scientific research or education," 35 U.S.C. 202(a), (c)(7)(B) and (C). The contractor must also ensure that any assignee that is granted the "exclusive right to use or sell any subject invention" agrees that any products made using the subject invention will be

"manufactured substantially in the United States" unless the government waives that condition. 35 U.S.C. 204.

The government is entitled to an irrevocable, paid-up license from the contractor to practice a federally funded invention. 35 U.S.C. 202(c)(4). The government may keep title or otherwise restrict a contractor's title when particularly sensitive governmental interests are at stake, such as when a contractor is controlled by a foreign government or the research relates to foreign intelligence, nuclear propulsion, or nuclear weapons programs. 35 U.S.C. 202(a)(i)-(iv). The government also retains "march-in" rights to subject inventions, meaning that it may step in to license the invention in certain circumstances, such as when a contractor fails to take steps to achieve practical application of the invention, or when public health or safety requires it. 35 U.S.C. 203.

If a contractor does not elect to retain title to a subject invention, the government may decide whether to take title for itself or allow title to pass to the inventor. In such circumstances, the federal agency "may consider"—"and after consultation with the contractor grant"—"requests for retention of rights by the inventor." 35 U.S.C. 202(d). The inventor's rights remain "subject to the provisions of this Act and regulations promulgated hereunder." *Ibid.*; see 37 C.F.R. 401.9. Thus, the inventor may receive title to the invention only when the contractor chooses not to retain title (or fails to comply with the applicable statutory prerequisites) and the government affirmatively authorizes the inventor to take title.

The Bayh-Dole Act "take[s] precedence over any other Act which would require a disposition of rights in subject inventions of small business firms or nonprofit organizations contractors in a manner that is inconsistent with" the disposition of rights in the Act. 35 U.S.C. 210(a). Thus,

unlike the pre-1980 experience with IPAs, when agencies like the NSF were required to conform their funding agreements to the Patent Act's allocation of rights, the Bayh-Dole Act explicitly gives precedence to the Act's own "[d]isposition of rights." 35 U.S.C. 202.

4. This case concerns the ownership of three patents for monitoring the effectiveness of treatments for human immunodeficiency virus (HIV). The patented process was developed by researchers at the Leland Stanford Junior University (Stanford) using federal funds. One of those scientists—Dr. Mark Holodniy—performed research both at Stanford and at Cetus Corporation (Cetus). Holodniy executed agreements with both Stanford and Cetus regarding rights in his inventions, and a dispute subsequently arose about the ownership of the patents at issue here.

In the early to mid-1980s, Cetus developed polymerase chain reaction (PCR) technology, a technique for making billions of copies of specific sequences of DNA from a small number of starting molecules. Pet. App. 32a. In 1988, Cetus and Stanford began collaborating on the use of PCR in HIV/AIDS research. *Ibid.* That year, Holodniy began conducting research at Stanford's Center for AIDS Research. *Ibid.* Holodniy signed a "Copyright and Patent Agreement" with Stanford, *id.* at 118a-121a, in which he "agree[d] to assign or confirm in writing to Stanford * * * that right, title and interest in * * * such inventions," *id.* at 118a-119a.

In February 1989, Holodniy began making regular visits to Cetus to learn about PCR and to develop a PCR-based test for HIV. Pet. App. 4a. At Cetus, Holodniy signed a "Visitor's Confidentiality Agreement," *id.* at 35a-36a, in which he "assign[ed] to CETUS [his] right, title, and interest in" any inventions conceived or reduced to practice "as a consequence of [his] access to CETUS' facilities or

information," *id.* at 123a. Holodniy's research with Cetus produced an assay (procedure) for using PCR to measure the amount of HIV nucleic acids in blood samples from people infected with HIV. *Id.* at 5a, 37a. Holodniy published these findings with Cetus co-authors. *Ibid.*

Holodniy then returned to Stanford and worked with others on clinical studies to determine whether the assay could be used to judge the efficacy of anti-HIV drugs. Pet. App. 5a, 39a. That research demonstrated that PCR can be used to track the HIV RNA in a patient's bloodstream to assess the effectiveness of anti-HIV drugs the patient is taking. *Ibid.* Holodniy published this discovery with several Stanford and Cetus co-authors. *Id.* at 38a-39a. The research underlying the discovery was funded in part by the federal government through an agreement with Stanford. *Id.* at 5a, 109a, 114a-115a.

In 1992, Stanford submitted a patent application for this method of monitoring the effectiveness of anti-HIV treatment, which resulted in the issuance of the three patents at issue. Pet. App. 108a-109a. Holodniy and two other scientists are named as co-inventors of these patents, and Stanford is identified as their assignee. *Id.* at 4a, 125a, 127a, 129a. Stanford disclosed the invention to the federal government, specifying that the "invention was made with Government support" and that "[t]he Government has certain rights in th[e] invention," and it confirmed to the government the grant of an irrevocable, paid-up license to the invention. *Id.* at 5a-6a. In 1995, Stanford formally elected to retain title to the invention under the Bayh-Dole Act. *Id.* at 5a-6a, 115a-116a.

5. Ten years later, petitioner filed suit, alleging that respondents (who had purchased Cetus's PCR business) were marketing HIV detection kits that infringed its patents. Pet. App. 5a-6a, 31a. Respondents counterclaimed,

contending, *inter alia*, that they possessed ownership interests in the patents because of Holodniy's agreement with Cetus. *Id.* at 7a, 122a-124a.

The district court rejected respondents' claim of ownership on several grounds. As relevant here, the court held that Holodniy's assignment to Cetus was ineffective to convey an interest in the patents because, under the Bayh-Dole Act, he lacked any such interest to convey. Pet. App. 61a. The court explained that when "the individual inventor is not a contracting party," "the Bayh-Dole Act provides that the individual inventor may obtain title only after the government and the contracting party have declined to do so." *Ibid.* (citing 35 U.S.C. 202(d)). Because "Stanford exercised its right and obtained title in the patents" under the Bayh-Dole Act, the court concluded, Holodniy "had no interest to assign to Cetus." *Id.* at 62a.

In a later proceeding, however, the district court held that the patents were invalid for obviousness. See *Board of Trs. of Leland Stanford Jr. Univ.* v. *Roche Molecular Sys., Inc.*, 563 F. Supp. 2d 1016, 1040-1049 (N.D. Cal. 2008). Petitioner appealed that decision, and respondents cross-appealed on the ownership issue. Pet. App. 2a-3a.

6. The court of appeals affirmed in part, vacated in part, and remanded. Pet. App. 1a-28a. As relevant here, the court held that petitioner had obtained no ownership interests in the patents from Holodniy because Holodniy had assigned his patent rights to Cetus, leaving nothing for him to assign to Stanford. *Id.* at 27a. The court explained that the agreement between Holodniy and Stanford, in which Holodniy "agree[d] to assign or confirm in writing" any invention he conceived or reduced to practice while at Stanford, was merely a promise to assign his rights "to Stanford at an undetermined time." *Id.* at 13a. By contrast, the court viewed Holodniy's agreement with

Cetus—in which Holodniy stated that he "will assign *and do[es] hereby assign* to CETUS" his interest in inventions conceived as a consequence of his access to Cetus facilities and information—as "effect[ing] a present assignment" to Cetus of his future inventions. *Id.* at 14a (emphasis added). The court concluded that "Cetus's legal title vested first" and that Holodniy therefore had no rights to assign to Stanford with respect to the pertinent inventions. *Ibid.*

The court of appeals rejected petitioner's contention that the Bayh-Dole Act gave Stanford title to the patents. Pet. App. 18a-21a. In the court's view, the Bayh-Dole Act was relevant only to determine what residual rights Stanford and the government might have after effectuating the assignments in the Holodniy-Stanford and Holodniy-Cetus agreements. *Id.* at 19a-20a. The court stated that "Stanford was entitled to claim whatever rights were still available after the Government declined to exercise its option, including the rights of [Holodniy's co-authors on the patents]," but that Holodniy had already assigned his rights to Cetus. *Id.* at 19a. The court explained that Holodniy "still possessed rights at the time he signed the [agreement] with Cetus" and that the Act did not "automatically void the patent rights that Cetus received from Holodniy." *Id.* at 19a, 21a.

The court of appeals concluded that petitioner lacked standing to pursue the infringement claim because it had not acquired Holodniy's interest in the patents and, under Federal Circuit precedent, all co-owners must join as plaintiffs in an infringement suit. Pet. App. 27a. Based on its determination that petitioner lacked standing to pursue the claim, the court vacated the district court's judgment that the patents were invalid. *Id.* at 27a-28a.

7. Petitioner filed a petition for rehearing and rehearing en banc, which the court of appeals denied. Pet. App. 75a-77a.

DISCUSSION

The court of appeals erred in holding that an individual inventor may contract around the Bayh-Dole Act's framework for allocating ownership of federally funded inventions. Under the Act, title to a subject invention vests in the contractor (*i.e.*, the research institution), and the contractor may "elect to retain [that] title." 35 U.S.C. 202(a). An individual inventor can obtain title in a federally funded invention only if the contractor declines to take title (or fails to assert its statutory rights as required by the Act) and the government affirmatively authorizes the retention of title by the inventor. 35 U.S.C. 202(d). Here, Holodniy had no patent rights to assign to Cetus because title to the inventions initially vested in Stanford and Stanford exercised its Bayh-Dole Act rights. The court of appeals' decision—which holds that Holodniy's assignment to Cetus limited the patent rights that Stanford could assert under the Bayh-Dole Act—turns the Act's framework on its head.

The question presented is important. The Bayh-Dole Act reflects Congress's considered judgment about the best way to ensure that federally funded inventions are made available to the public and to encourage further science and technology research and development in the United States. The court of appeals' decision ignores that judgment and allows the wishes of a single inventor to override the Act's allocation of rights in federally funded inventions. The funds at issue are substantial: the federal government spends billions of dollars per year on science and technology research at United States colleges and universities, small businesses, and nonprofit organizations.

This case is a suitable vehicle for resolving the question presented. The question presented is a pure matter of law, and the decision below has created immediate and substantial uncertainty about title to federally funded inventions. This Court's review of this important question is therefore warranted.

A. The Court Of Appeals Misconstrued The Bayh-Dole Act's Comprehensive Framework For Disposition Of Rights In Federally Funded Inventions

The Bayh-Dole Act replaced a welter of agency-specific statutes and funding agreements with a unified statutory framework for allocating rights in federally funded inventions. The court of appeals' decision upsets the balance struck by Congress and allows individual inventors to control the disposition of rights in federally funded inventions.

1. With respect to federally funded inventions, the Act establishes a statutory hierarchy of rights among the government, contractors, and inventors. The Act grants priority of title to the contractor by giving the contractor the statutory right to "elect to retain title" in the invention. 35 U.S.C. 202(a). Through this provision, the Act "establishes a presumption that ownership of all patent rights in government funded research will vest in [the] contractor," *House Report* 5, unless the contractor declines to retain title or fails to assert its rights. Under the Bayh-Dole Act, the contractor's ability to assert its statutory prerogatives does not depend on an assignment of rights by the individual inventor.

In certain circumstances, such as when the research to be performed under a particular funding agreement implicates especially sensitive government interests, the government may provide in the agreement that title to any resulting inventions will vest in the government. 35 U.S.C.

202(a). The government also has specific statutory rights relating to the invention, such as licensing and march-in rights. 35 U.S.C. 202(c)(4), 203. But the contractor's decision to retain title controls unless the government has retained title through a funding agreement or the contractor fails to exercise its rights in the manner and within the time specified in the Act. 35 U.S.C. 202(a) and (c)(1)-(3).

The inventor may exercise rights in the invention only in limited circumstances—namely, when the contractor declines to retain title (or fails to exercise its rights under the Act) and the government funding agency decides, after consultation with the contractor, to grant the inventor's request for rights. 35 U.S.C. 202(d). Thus, the inventor occupies the lowest position in the Bayh-Dole Act's hierarchy of rights in federally funded inventions, subordinate both to the contractor and the federal government. See, *e.g.*, *Platzer* v. *Sloan-Kettering Inst. for Cancer Research*, 787 F. Supp. 360, 364-365 (S.D.N.Y. 1992) (concluding that "the intended beneficiaries of the Bayh-Dole Act are the [research] institutions themselves and the government," not the inventors).

The Bayh-Dole Act permitted Holodniy to assign to Cetus the same rights Holodniy himself would otherwise have possessed. With respect to any patentable invention that Holodniy might ultimately conceive or reduce to practice with the assistance of federal funds, however, Holodniy possessed only a contingent interest in obtaining title to the invention *if* the contractor waived or failed to exercise its rights under the Act and the government then authorized Holodniy to retain title. As events transpired, Stanford elected to retain title and complied with the statutory requirements for doing so, Pet. App. 5a-6a, so that contingent

interest was of no practical value.[1] And while nothing in the Bayh-Dole Act precluded Holodniy from assigning his own contingent interest to Cetus, Holodniy could not assign to Cetus any higher priority in the federally funded inventions than Holodniy himself would have possessed.

The court of appeals framed the question presented as whether Stanford's "election of title under Bayh-Dole had the power to void any prior, otherwise valid assignment of patent rights." Pet. App. 19a. Stanford's entitlement to retain title to the patented inventions, however, does not depend on the view that the Bayh-Dole Act "void[ed]" Holodniy's assignment of rights to Cetus. Holodniy assigned to Cetus *his own* "right, title, and interest in" any inventions conceived or reduced to practice "as a consequence of [his] access to CETUS' facilities or information," *id.* at 123a; but the parties to that agreement surely understood that the scope of Holodniy's rights in any later-developed inventions would be determined under applicable law. If Holodniy's eventual contributions to the research that produced the patented inventions had been too insignificant to justify treating him as a co-inventor, for example, Cetus would have acquired no rights in those inventions because Holodniy would have had no such rights to assign. Similarly here, the Bayh-Dole Act did not "void" Holodniy's assignment to Cetus of all his rights in the relevant inventions; it simply limited, to the contingent interests de-

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[1] Under 35 U.S.C. 202(c)(7)(B), a nonprofit organization that retains title to a federally funded invention under the Bayh-Dole Act must share any royalties with the inventor. To the extent that Holodniy would otherwise be entitled to a share of royalties pursuant to that provision, that right would potentially be assignable to Cetus. Neither the parties nor the courts below have suggested, however, that any such royalties are in dispute.

scribed above, the rights that Holodniy could potentially assign.

2. The court of appeals' decision turns the Bayh-Dole Act's hierarchy on its head. In the court's view, title to a federally funded invention belongs in the first instance not to the university, but to the inventor. The court stated that Holodniy "still possessed rights [in the invention] at the time he signed the [agreement] with Cetus," Pet. App. 19a, and it determined that Stanford's and the government's rights were subordinate to Holodniy's assignments, *id.* at 13a-18a. The court considered the government's rights second, stating that "when the Bayh-Dole Act's provisions are violated, 'the government can choose to take action * * * [but] title remains with the named inventors or their assignees.'" *Id.* at 18a-19a (quoting *Central Admixture Pharmacy Servs., Inc.* v. *Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347, 1352-1353 (Fed. Cir.), cert. denied, 552 U.S. 1038 (2007)). The court put the contractor's rights last, stating that Stanford could only "claim whatever rights were still available after the Government declined to exercise its option." *Ibid.*

As a result, the court determined that an inventor like Holodniy may preclude a contractor from obtaining its statutory ownership interests in a federally funded invention simply by making a present assignment of rights to a third party. See Pet. App. 19a. Thus, under the decision below, which entity retains rights to a federally funded invention depends on the fortuity of whether the inventor assigned his rights, and whether that assignment came before the contractor's election of title—contrary to the uniform scheme for the allocation of patent rights in federally funded inventions that the Bayh-Dole Act was intended to establish.

3. The court of appeals' decision also ignores the Bayh-Dole Act's statement that "[t]his chapter [*i.e.*, 35 U.S.C. 200 *et seq.*] shall take precedence over any other Act which would require a disposition of rights in subject inventions * * * in a manner that is inconsistent with this chapter." 35 U.S.C. 210(a). Under the Patent Act (as under the common law), the right to patent an invention generally belongs to the inventor, who may assign that right. See 35 U.S.C. 101, 115, 116, 261; see also Pet. App. 19a-20a. By its plain terms, however, the Bayh-Dole Act "take[s] precedence over" that allocation, 35 U.S.C. 210(a), with respect to the federally funded inventions to which it applies. Thus, even assuming that Holodniy's assignment of Patent Act rights to Cetus would otherwise prevail over his assignment to Stanford, the priority rules set forth in the Bayh-Dole Act are controlling here.

B. The Question Presented Is Important And Warrants This Court's Review

The decision below raises an important question about the scope of a federal statute that applies to thousands of colleges and universities, small businesses, and nonprofit organizations across the United States and implicates billions of dollars per year in federal funding from a variety of government agencies.

1. Congress enacted the Bayh-Dole Act to replace a patchwork of varied statutory and agency approaches to ownership of federally funded inventions with a uniform and effective framework. *House Report* 3 (explaining that universities and small businesses were unable to "cope with the bewildering regulatory and bureaucratic problems associated with" the prior regime). Through the Act, Congress "establishe[d] a presumption that ownership of all patent rights in government funded research will vest in

any contractor who is a non-profit research institution or a small business." *Id.* at 5. Since 1980, contractors have generally understood that they may obtain good title to federally funded inventions, subject to certain rights retained by the government, by complying with the Act's requirements. See *The Bayh-Dole Act—The Next 25 Years: Hearing Before the Subcomm. on Technology and Innovation of the H. Comm. on Science and Technology*, 110th Cong. 1st Sess. 4-5 (2007); AAU Amicus Br. 2-3.

The court of appeals' decision upsets those settled expectations. Under the decision below, even when a contractor elects to retain title and complies with the requirements of the Act, an inventor may defeat that title by making an assignment to a third party, the terms or even existence of which may be unknown to the contractor at the time of the election and for years thereafter. Further, the question of which entity ultimately takes title may depend on variations in assignment language or the timing of inconsistent assignments. See WARF Amicus Br. 11. The decision below creates serious uncertainty about contractors' title to patents, raising the cost of due diligence for contractors and potential licensees, and making it difficult and risky for contractors to give potential licensees or investors warranties of good title to patents obtained through the Bayh-Dole Act framework.

2. The decision below also frustrates Congress's efforts to foster scientific research and development in the United States and to use federally funded inventions to benefit American workers. Congress required that non-profit contractors use "the balance of any royalties or income earned * * * for the support of scientific research or education," 35 U.S.C. 202(c)(7)(C), and ensure that any assignee granted the "exclusive right to use or sell any subject invention" agrees to manufacture any products using the subject

invention "substantially in the United States" unless the government waives that condition, 35 U.S.C. 204. Under the decision below, an inventor may assign rights in a federally funded invention to a third party outside of the Act, thereby sidestepping those requirements.

The court of appeals' decision also calls into question the government's ability to manage federally funded inventions for the benefit of the public. The Act provides that, if a contractor does not take sufficient action to achieve practical application of the invention, is not adequately satisfying a public health or safety need related to the invention, or has not ensured that assignees with exclusive rights manufacture products using the invention substantially in the United States, the agency may "march in" and require the contractor to grant licenses to third parties. 35 U.S.C. 203. Those rights are a valuable tool to ensure that federal funding for research ultimately promotes the public interest, because they help provide "leverage to promote commercialization of federally funded inventions." *GAO Report* 9-12. Those rights would be jeopardized by the inventor's ability to assign rights in the invention outside of the Act's framework.

3. The amount of federal funding at issue is substantial. The federal government funds over half of all scientific and technical research conducted at colleges and universities in the United States. *GAO Report* 1; NSF, NSF 10-311, *Academic R&D Expenditures: FY 2008*, at 8 & tbl. 1 (2010) (*NSF Report*). In 2008, that amounted to more than $31 billion in federal funds. *NSF Report* 8 & tbl. 1; see Donna Fossum et al., *Innovation in Academe: Federal R&D Funding and the Patenting Activities of U.S. Universities and Colleges* 5-8 tbl. 2.1 (2009) (*RAND Report*) (listing federal research and development funding for top 100 colleges and universities). And that figure does not account for the

billions of dollars of federal funds provided each year to small businesses and nonprofit organizations. That funding is crucial to scientific and technological innovation, as the amount of federal research funds an institution receives strongly correlates with the number of patented inventions it generates. *RAND Report* 19; AAU Amicus Br. 18-20; MIT Amicus Br. 7-8. The decision below allows individual inventors to allocate the benefits of federally funded research to third parties through individual contract assignments, rather than to contractors and to the public, as Congress intended. The "enormous" sum of federal funds at issue here is another "strong factor" counseling in favor of certiorari. *Fidelity Fed. Bank & Trust* v. *Kehoe*, 547 U.S. 1051, 1051 (2006) (Scalia, J., joined by Alito, J., concurring in the denial of certiorari); see Eugene Gressman et al., *Supreme Court Practice* 269 (9th ed. 2007).

C. This Case Is An Appropriate Vehicle For Resolving The Question Presented

1. The court of appeals definitively resolved a pure question of law. Its resolution of this question was not dependent on the particular facts of this case. The court held that patent rights to a federally funded invention vest initially in the inventor, not the contractor, and that the inventor's transfer of rights to a third party effectively negates the contractor's otherwise timely election of rights under the Bayh-Dole Act. Pet. App. 18a-21a. That holding casts serious doubt on the ownership of a very substantial number of federally funded inventions. Certiorari is warranted on that basis. See, *e.g.*, *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002).

The Court should not await further consideration of the issue in the lower courts. Although questions regarding an individual's or a company's interest in a federally funded

invention could conceivably arise in any type of property dispute, such issues typically have arisen in suits involving patent validity and infringement claims or contract claims against the United States, matters within the exclusive jurisdiction of the Federal Circuit. See, *e.g.*, *Central Admixture*, 482 F.3d at 1349-1352; *Campbell Plastics Eng'g & Mfg., Inc.* v. *Brownlee*, 389 F.3d 1243, 1244-1246 (Fed. Cir. 2004); see also 28 U.S.C. 1295. And because the Federal Circuit declined to rehear this case en banc, further percolation of the issue in that court is unlikely.

2. Contrary to respondents' suggestion (Br. in Opp. 15), contractors and the government cannot terminate the damage the Court below did to the Bayh-Dole Act scheme by modifying their assignment clauses in future contracts. Changing future contracts will not change the allocation of rights for the massive number of past and present agreements relating to ongoing or completed research over the three decades since the Act took effect. See Pet. 17-18. And even with respect to future contracts between universities and individual researchers, it is far from clear that a university can adequately protect its Bayh-Dole Act prerogatives simply by insisting on a present assignment of rights from the researcher. The university would still run the risk, for example, that the researcher had *already* assigned his rights to a third party, and that the earlier-in-time assignment would be found controlling.

Respondents' other arguments against certiorari are unpersuasive. Although respondents suggest (Br. in Opp. 20-21) that the invention at issue was not conceived or reduced to practice with federal funds, the court of appeals appeared to decide the case on the assumption that it was, see Pet. App. 5a, and this Court should do the same, see, *e.g.*, *Hudson* v. *Michigan*, 547 U.S. 586, 590 (2006). Respondents also contend (Br. in Opp. 17) that the question

presented may not be outcome-determinative here, since respondents might ultimately prevail on alternative grounds (*e.g.*, that the relevant patents are invalid) even if the court of appeals' Bayh Dole Act ruling is reversed. But the court decided an important statutory question in a manner that upset decades of settled expectations, and the issue is sufficiently important to warrant this Court's review now.

Respondents also note (Br. in Opp. 11) that petitioner has not been deprived of all rights in the inventions because it obtained valid assignments from Holodniy's co-inventors. But petitioner's retention of rights in the patents through Holodniy's co-inventors is a fortuity; the court of appeals did not premise its analysis on that fact or condition its legal holding upon it. Respondents similarly contend (*id.* at 13) that this case is not important because it presents no issue of government patent rights. That likewise depends on the fortuity that Stanford was able to obtain rights through Holodniy's co-inventors and grant the government a license to practice the invention based on those rights. Because the court of appeals' flawed construction of the Bayh-Dole Act will be binding precedent in the Federal Circuit even in cases where the sole inventor of a federally funded invention assigns his rights to a third party, the presence of ameliorating circumstances in this particular case does not meaningfully reduce the practical impact of the decision.

3. Finally, respondents note (Br. in Opp. 14) the court of appeals' suggestion (Pet. App. 20a n.1) that the government may have "some other legal recourse" against an inventor who assigns to a third party all rights in a federally funded invention. But as respondents recognize (Br. in Opp. 2), the Federal Circuit's decision depends on the view that "the Bayh-Dole Act nowhere alters an inventor's basic freedom to assign his own rights in an invention to a third

party." By upending the Bayh-Dole Act's hierarchy of rights, the court of appeals necessarily made the government's rights, like the contractor's rights, depend on the actions of an individual inventor. This Court should grant review now to correct the court of appeals' serious misunderstanding of the Bayh-Dole Act's framework for determining ownership of federally funded inventions.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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Supreme Court of the United States

BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY,

Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., et al.,

Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF OF *AMICI CURIAE* ASSOCIATION OF AMERICAN UNIVERSITIES, ASSOCIATION OF AMERICAN MEDICAL COLLEGES, ASSOCIATION OF PUBLIC AND LAND-GRANT UNIVERSITIES, THE ASSOCIATION OF UNIVERSITY TECHNOLOGY MANAGERS, COUNCIL ON GOVERNMENTAL RELATIONS, IN SUPPORT OF PETITIONER

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INTEREST OF *AMICI CURIAE*[1]

Amici are leading research universities and associations of universities involved in the research and development of a wide range of technologies. *Amici* have thirty years of experience under the Bayh-Dole Act and are keenly aware of the threat the court of appeals' decision poses to the Act's success.

SUMMARY OF ARGUMENT

"[F]ederal support accounts for over half of the research conducted at colleges and universities in the United States."[2] Even according to conservative estimates, university patent licensing has produced astounding economic benefits – from 1996 to 2007, university licensing contributed an estimated $187 billion to U.S. gross domestic product, achieved a

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[1] The parties have consented to the filing of this brief. Counsel of record for all parties received notice at least 10 days prior to the due date of *amici curiae's* intention to file this brief. No counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici curiae*, their members, or their counsel made a monetary contribution to its preparation or submission.

[2] Gov't Accountability Office, GAO-09-742, *Information on the Government's Right to Assert Ownership Control over Federally Funded Inventions* 1 (2009) (hereinafter "GAO Report").

$457 billion impact on U.S. gross industrial output, and created 279,000 new jobs.[3]

The Bayh-Dole Act, 35 U.S.C. §§ 200-212, which provides the framework for commercialization of federally funded research at universities, stands as one of the most effective statutes ever passed by Congress. One commentator called the Act "[p]ossibly the most inspired piece of legislation to be enacted in America over the past half-century" and suggested that "[m]ore than anything, this single policy measure helped to reverse America's precipitous slide into industrial irrelevance." *Innovation's Golden Goose*, 365 The Economist 3, 3 (2002).

The Act provides for the disposition of rights in a predictable and reliable way that allows universities and other nonprofit institutions to acquire clear title and license the inventions for development while at the same time reserving important rights for the federal government. The uniformity and clarity provided by the Act are among its principal achievements and are essential to the statutory purpose of promoting the advantageous utilization of inventions derived from federally funded research. *See* Council on Governmental Relations, *The Bayh-Dole Act: A Guide to the Law and Implementing Regulations* 9

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[3] *See* David Roessner *et al.*, *The Economic Impact of Licensed Commercialized Inventions Originating in University Research, 1996-2007* 7-8 (2009), *available at* http://www.bio.org/ip/tech transfer/BIO_final_report_9_3_09_rev_2.pdf.

(1999), *available at* http://www.unm.edu/~counsel/files/DOC057.PDF ("Certainty of title to inventions made under federal funding is perhaps the most important incentive for commercialization."); GAO Report, *supra*, at 4. The statute has been so effective at efficiently disposing of patent rights that, until the decision of the court of appeals in this case, the Act has attracted little controversy, and consequently little judicial attention, despite its critical role in the most dynamic areas of the American economy.

The court of appeals' opinion, if not corrected by this Court, threatens that success story by casting in doubt the rights of universities and the federal government alike to inventions arising from hundreds of billions of dollars in research. The decision of the court of appeals turns the statutory structure on its head, allowing rights in federally funded patents to be disposed of in obscure private contracts between researchers and third parties rather than according to Congress's dictates. Bayh-Dole provides for a "[d]isposition of rights" in federally funded inventions, 35 U.S.C. § 202 (title), and establishes a presumption that ownership is allocated to the university or other nonprofit, 35 U.S.C. § 202(a). Individual researchers are allocated rights of ownership only if both the university and the federal agency providing the funding decline to take title. 35 U.S.C. § 202(d). The court of appeals, by contrast, held that the ownership rights of the university are subject to being defeated by the inventor, operating outside the statute.

By the same reasoning, the federal government's own rights and interests are subject to circumvention at the whim or by the inadvertence of an individual inventor. The court of appeals' refusal to enforce Bayh-Dole places at risk, for instance, the government's right under the statute to reserve title to itself in certain instances, to take title from a nonprofit that violates the Act's provisions, to receive a license to practice the invention, and to require the nonprofit to grant a license to a third party under circumstances specified in the Act. *See* 35 U.S.C. §§ 202(a), (c), 203, 204. It also undermines the strong federal interest in promoting commercialization through uniform, clear, and efficient allocation of title to federally funded inventions. *See* 35 U.S.C. § 200; S. Rep. No. 96-480, at 21 (1979).

The consequences of the court of appeals' decision are dramatic. Universities cannot simply rewrite assignment documents with all of their researchers going forward in time, because hundreds of billions of dollars in federally funded inventions will be entering the market during the next 10 to 15 years based on already-executed assignment documents. *See* GAO Report, *supra*, at 6-7. Private industry cannot be expected to invest billions of dollars over 10 to 15 years to transform fundamental breakthroughs at universities into commercial products (and jobs) without knowing that title to the inventions is free from reasonable question. Roche will likely urge the Court to wait until the consequences of clouded title are measured and weighed. But delay itself will have

a considerable detrimental effect on universities, federal funding agencies, and the U.S. economy. The Court should grant the petition for certiorari and correct the court of appeals' fundamentally flawed decision.

ARGUMENT

I. OWNERSHIP OF FEDERALLY FUNDED INVENTIONS IS ALLOCATED ACCORDING TO BAYH-DOLE

The court of appeals erroneously analyzed this case as one of dueling contracts. The court first assessed the "chain of title" in the invention as a question of contract interpretation, *i.e.*, whether priority should be given to the assignment in the employment agreement between Stanford and its faculty researcher Dr. Holodniy (confirmed at the time of the patent application) or the assignment contained in a Visitor Confidentiality Agreement ("VCA") between Holodniy and a third-party lab, Cetus. *See* Pet. App. 12a-15a.[4] The court concluded that Stanford's "agree to assign" framework creates only a promise to assign rights in the future whereas, under the VCA, "Cetus immediately gained equitable title to Holodniy's inventions." *Id.* at 13a-14a. Holodniy therefore "ha[d] nothing remaining to

[4] Roche Molecular Systems, Inc. and related respondents ("Roche") are successors to Cetus's agreement with Holodniy.

assign" to Stanford at the time of its patent application. *Id.* at 14a (quoting *FilmTec Corp.* v. *Allied-Signal, Inc.*, 939 F.2d 1568, 1572 (Fed. Cir. 1991)). Only after so concluding did the court consider the possible effect of Bayh-Dole, asking whether Stanford's "election of title under Bayh-Dole had the power to void any prior, otherwise valid assignments of [Holodniy's] patent rights." *Id.* at 19a. Instead, the court should have started with Bayh-Dole and asked whether Holodniy could assign rights to Cetus in derogation of Stanford's statutory rights.

Bayh-Dole, not side-agreements between individual researchers and third parties, governs the allocation of rights in federally funded inventions. The Act specifies, for example, that nonprofits "acquire[ ] title under this chapter" of the U.S. Code, 35 U.S.C. § 203(a), and that inventors' ownership rights, which must be approved by the federal agency, are "subject to the provisions of this Act," 35 U.S.C. § 202(d). It is evident from a careful analysis of the statutory text and structure, as well as the broader legal context, that Holodniy could assign to Cetus only limited, contingent rights that could not defeat the superior rights allocated to Stanford and the federal government under the Act.

A.1. Section 202, entitled "Disposition of rights," specifies the relative rights of the government, nonprofit contractors, and individual inventors in federally funded inventions. 35 U.S.C. § 202. Subsection (a) establishes the general rule that "[e]ach nonprofit organization or small business firm

may . . . elect to retain title to any subject invention." 35 U.S.C. § 202(a); *see also* S. Rep. No. 96-480, at 36 (reprinting letter from the Congressional Budget Office) ("The bill would *automatically grant* small businesses and nonprofits *title* to inventions arising from Government-supported research unless the contracting agency could justify . . . holding title to the invention.") (emphasis added). The same subsection permits the federal government to reserve title to itself in specified circumstances – for instance, when the funding contract concerns weapons-related programs or foreign intelligence activities. 35 U.S.C. § 202(a)(i)-(iv).

When, as is usually the case, title is allocated to the nonprofit, the nonprofit's rights are "subject to the provisions of paragraph (c)" of § 202 and "the other provisions of" the Act, 35 U.S.C. § 202(a), that reserve important rights to the government and impose other restrictions on the nonprofit to "meet the needs of the Government and protect the public" interest in the federally funded invention, 35 U.S.C. § 200. Under those provisions, the government agency has discretion to take title to the invention if the contracting nonprofit fails timely to disclose the invention to the government, to elect title, or to file necessary patent applications. 35 U.S.C. § 202(c)(1)-(3); *see Campbell Plastics Eng'g & Mfg., Inc.* v. *Iæs Brownlee*, 389 F.3d 1243, 1249 (Fed. Cir. 2004) (failure to disclose invention properly resulted in forfeiture of patent ownership to the funding agency). The government also receives a non-exclusive,

non-transferable, irrevocable, paid-up license to practice the invention and may prohibit a nonprofit from assigning rights in the invention. 35 U.S.C. § 202(c)(4), (c)(7)(A). The contractor, for its part, is obligated to make reasonable efforts to achieve practical application of the invention and to report its efforts to the government, to give preference to small businesses and U.S. industry, to share royalties with the inventor, and to utilize excess royalties to fund further research or education. 35 U.S.C. §§ 202(c)(5), (c)(7)(B)-(D), 203, 204. In certain exceptional circumstances, the government is entitled to "march in" and require the contractor to grant a license to a third party. 35 U.S.C. § 203(a).

Section 202 also specifies the circumstances under which rights to a federally funded invention will be allocated to the inventor and the limitations on those rights. Subsection (d) provides that "[i]f a contractor does not elect to retain title to a subject invention . . . the Federal agency may consider and after consultation with the contractor grant requests for retention of rights by the inventor subject to the provisions of this Act and regulations promulgated hereunder." 35 U.S.C. § 202(d). Thus, the statutory text makes clear that an inventor can exercise ownership rights in the invention only if two circumstances are met: (1) the contractor does not exercise its superior right to take title and (2) the federal agency affirmatively grants a request by the inventor. *Ibid.*; *Fenn* v. *Yale Univ.*, 184 Fed. Appx. 21, 22 (2d Cir. 2006) (summary order) ("[A] federal agency . . .

may only grant an inventor's request to retain rights to an invention subject to the Act when the contractor . . . has elected not to retain [the] rights."). Moreover, even when permitted to take title, the inventor does so "subject to the provisions of this Act and regulations promulgated hereunder." 35 U.S.C. § 202(d). By regulation, the Secretary of Commerce has specified that an agency that allows the inventor to retain ownership rights pursuant to Section 202(d) "will impose" certain conditions upon the inventor. 37 C.F.R. § 401.9. Those conditions include requirements that the inventor convey title to the government if he fails timely to disclose the invention to the government or to prosecute or maintain the patent rights, and the government's right to compel licensing of the invention in certain circumstances in which the inventor has failed to utilize the invention or failed to secure an agreement that products embodying the invention will be produced in the United States. *Ibid.*; 37 C.F.R. § 401.14(a) (standard clause ¶¶ (d)(1), (d)(3), (i), (j)).

It is therefore clear from the Act's text that Holodniy could not convey to Cetus rights that were superior to Stanford's. Under the Act, Holodniy could exercise rights in the invention *only* if Stanford chose not to exercise its right to assert ownership *and* the funding agency *granted* an application by Holodniy to retain ownership. Holodniy's rights, and all that he could assign to Cetus, were therefore doubly contingent. Because neither of the necessary contingencies occurred – Stanford elected title, and the agency did

not grant Holodniy permission to retain ownership (which Holodniy never requested) – Cetus could not have obtained any actual ownership rights by assignment from Holodniy.

2. The court of appeals, by contrast, regarded Bayh-Dole as "regulat[ing] relationships of small business and nonprofit grantees with the Government, not between grantees and the inventors who work for them." Pet. App. 21a (quoting *Fenn* v. *Yale Univ.*, 393 F. Supp. 2d 133, 141-42 (D. Conn. 2004), *aff'd*, 184 Fed. Appx. 21 (2d Cir. 2006)). Thus, in the court's view, before the Act could allocate rights between the government and Stanford, Stanford must first receive an assignment of rights from Holodniy, a question of state and Federal Circuit contract law. *Id.* at 12a, 21a. But that understanding cannot be squared with the text and structure of the Act. Under the Act, as discussed above, the inventor must apply for and receive permission from the federal agency before he can retain ownership rights in a federally funded invention. 35 U.S.C. § 202(d). Moreover, if the agency consents, it "will impose" conditions on the inventor's rights. 37 C.F.R. §§ 401.9, 401.14(a) (standard clause ¶¶ (d)(1), (d)(3), (j)). The statute's recognition of the agency's discretion to "grant [inventor] requests for retention of rights" and the regulation's "impos[ition]" of conditions on the inventor if the agency does grant a request necessarily presume that the inventor's right to exercise ownership of the patent is conditioned by "the provisions of [the] Act." 35 U.S.C. § 202(d); 37 C.F.R. § 401.9. The

court of appeals' view that Holodniy could assign ownership of a federally funded invention to a third party, thereby trumping Bayh-Dole's allocation of rights, contradicts the Act's text and structure.

B. The conclusion that rights in federally funded inventions are determined according to the Bayh-Dole framework, and not by side-agreements entered into (perhaps inadvertently) by individual researchers, is further supported by the larger legal context within which Bayh-Dole was adopted. The apparent assumption of the court of appeals that an individual inventor has unfettered discretion whether and how to assign rights in federally funded inventions is incorrect. As other federal funding statutes make clear, and the Federal Circuit has elsewhere recognized, Congress can allocate ownership in federally funded inventions, rendering invalid any contrary purported assignment by the inventor. Bayh-Dole did not grant to individual researchers the power – that did not previously exist – to frustrate federal policy by assigning federally funded inventions to third parties. The erroneous interpretation of the court of appeals in this case would allow just that.

1. Congress has the preeminent role in establishing the system for patenting inventions that derive from federally funded research. All patent rights ultimately derive from federal statute. The Constitution provides that "The Congress shall have Power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective

Writings and Discoveries." U.S. Const. Art. I, § 8, cl. 8. Thus, the exclusive rights secured by patents owe their existence solely to the acts of Congress, and are therefore subject to such limitations as Congress imposes. Where Congress also provides the funding for the research from which an invention derives, its authority to control the disposition of patent rights in the invention is even clearer.

In numerous statutes that pre-dated Bayh-Dole, Congress allocated ownership of federally funded inventions to the federal government itself by force of law, independent of any assignment from the individual inventor. Several statutes specified that "title to such invention shall vest in the United States, and if patents on such invention are issued they shall be issued to the United States" unless waived. 42 U.S.C. § 5908(a) (1976) (Department of Energy);[5] *see also* 42 U.S.C. § 2182 (1976) ("[a]ny invention or discovery . . . shall be vested in, and be the property of" the federal agency that funded the research unless the agency "waive[d] its claim") (Nuclear Regulatory Commission); 42 U.S.C. § 2457(a) (1976) (NASA). Such statutes, without question, vested title in the United States unless the

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[5] Several additional statutes incorporated Section 5908 by reference. *See* 7 U.S.C. § 178j (Supp. II 1979); 42 U.S.C. § 5585(b) (Supp. II 1979); 42 U.S.C. § 6981(c)(3) (1976); 42 U.S.C. § 7879 (Supp. II 1979), *repealed by* Water Resources Research Act of 1984, Pub. L. No. 98-242, §§ 109-110(a), 98 Stat. 97, 101 (codified at 42 U.S.C. § 10308) (also incorporating Section 5908).

United States waived the rights in favor of the contractor or inventor.

As the Federal Circuit recognized in a case involving a pre-Bayh-Dole funding agreement, such pre-Bayh-Dole statutes "clearly provide[d] that title to any invention made or conceived under a [covered] contract 'shall vest' in the United States." *FilmTec Corp.* v. *Hydranautics*, 982 F.2d 1546, 1550 (Fed. Cir. 1992) (construing 42 U.S.C. § 5908 (as incorporated by the Saline Water Conversion Act, 42 U.S.C. § 1959d note (1976) (repealed 1978))). Thus, the court held, the inventor's purported assignee lacked standing to sue on the patent because the inventor "had no right to assign it." *Id.* at 1553. Rather, "title to inventions made by an employee hired to perform [federally funded] research automatically vested in the United States" by "operation of law." *Ibid.*

2. The court of appeals' decision in this case creates an unwarranted inconsistency – individual inventors have the power to frustrate the federal government's allocation of rights in federally funded inventions developed under contracts with nonprofits or small businesses, which are governed by Bayh-Dole, but have no such power with respect to inventions developed under contracts with other entities, such as large for-profit companies. Bayh-Dole displaces other statutes insofar as they relate to nonprofit organizations and small businesses by switching the presumption of ownership from the federal government to the nonprofit or small business. *See* 35 U.S.C. § 202(a); *id.* at § 210(a)

(providing that Bayh-Dole "shall take precedence over" any statute that "would require a disposition of rights" inconsistent with Bayh-Dole, including 21 listed statutes). However, the pre-Bayh-Dole statutes, such as Section 5908, continue to govern federally funded research with institutions other than nonprofits and small businesses. *See* 35 U.S.C. § 210(b).[6] *Hydranautics* makes clear that under such statutes, Holodniy's purported assignment to Cetus in the VCA could not defeat the federal agency's allocation of rights to Stanford. *See* 982 F.2d at 1548, 1553-54.

There is no indication that Congress intended Bayh-Dole to extend to individual inventors, in a dramatic departure from pre-Bayh-Dole statutes, the unilateral power to assign federally funded inventions outside the statutory structure. While Bayh-Dole marked an important policy shift vis-a-vis nonprofits and small businesses – adopting a presumption that they, rather than the federal government, would be allocated ownership of federally funded inventions – no significant change was contemplated with respect to the rights of inventors. To the contrary, although it differs in detail, Bayh-Dole, like its predecessors, permits "[d]isposition of

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[6] A Presidential Memorandum (endorsed by Congress, *see* 35 U.S.C. § 210(c)) has instructed federal agencies to use their waiver authority under the pre-Bayh-Dole statutes to extend Bayh-Dole's benefits to other federal contractors as well. *See* Memorandum on Government Patent Policy, Pub. Papers 248 (Feb. 18, 1983).

rights" in such inventions to individual inventors only pursuant to affirmative agency action and "subject to the provisions of" the Act. 35 U.S.C. § 202(d).

As demonstrated above, the court of appeals' view that Bayh-Dole concerns only the allocation of rights between the federal government and its contractors is therefore fundamentally flawed. The Act governs the disposition of rights among the federal government, nonprofit and small business contractors, *and* individual inventors. Holodniy could not assign to Cetus rights greater than those allocated to him under the Act. Because Holodniy's rights were doubly contingent, and neither contingency occurred, Cetus did not obtain ownership rights in the invention, and the court of appeals' judgment was in error.

II. THE COURT OF APPEALS' DECISION UNDERMINES THE CLEAR TITLE THAT IS CENTRAL TO BAYH-DOLE

Prior to Bayh-Dole's enactment, ownership of patent rights in federally funded research was governed by a convoluted combination of statutes, Executive Orders, federal regulations, funding agreements, assignment documents, and licenses. In general (subject to various exceptions), federal funding agencies acquired direct ownership of patents arising from federally funded research, unless the agency affirmatively decided to waive its rights. S. Rep. No. 96-480, at 2. It was nearly impossible, under that system, for nonprofits to obtain clear title to

inventions. As Congress ultimately concluded, that system failed to achieve the full promise of the research on which the federal government was spending so much money. Bayh-Dole establishes a uniform statutory framework under which nonprofits can obtain clear title to government funded inventions and attract private investment to commercialize the inventions. The Act has been immensely successful, but that success is cast in serious doubt by the court of appeals' decision, under which it is virtually impossible for universities to ensure clear title to their inventions.

A. Prior to Bayh-Dole's enactment, the lack of uniformity and clarity in the method for obtaining title to federally funded inventions presented a significant obstacle to the development of those inventions. *See* GAO Report, *supra*, at 4. Patent rights to government funded research were disposed of under twenty-six different regimes. *Ibid.*; H.R. Rep. No. 96-1307, pt. 1, at 3 (1980). This "potpourri" of policies "confus[ed] and discourage[d]" government contractors. Bradley Graham, *Patent Bill Seeks Shift to Bolster Innovation,* Wash. Post, Apr. 8, 1979, at M1. The Senate Report that accompanied Bayh-Dole recognized that uniformity and clarity were necessary to incentivize universities and small businesses to participate in government funding programs, as these private entities lacked the resources to cope with the existing maze of agency policies. *See* S. Rep. No. 96-480, at 2-3 (the complexity of "at least 24 different patent policies" that were "frequently contradictory"

"constitutes a very real hurdle to universities, nonprofit organizations, and small businesses who do not have large legal staffs to negotiate through this policy maze"). The multiplicity of approaches also made it difficult to ascertain clear title to inventions. The Senate Report recognized "the onerous burden of trying to determine the ownership of patents arising from the agencies' research and development grants and contracts." *Id.* at 30.

Moreover, government ownership of federally funded inventions did not encourage the investment in development necessary to realize those inventions' full potential. When Bayh-Dole was enacted, the federal government (through the individual funding agencies) owned between 25,000 and 30,000 patents. Graham, *supra,* at M2. Less than approximately 4% of those patents were developed for commercial use. *Ibid.*; *see also* GAO Report, *supra*, at 2.

Congress designed Bayh-Dole to "end this uncertainty [of patent ownership] and prevent these promising inventions from being suffocated under reams of unnecessary bureaucratic redtape." S. Rep. No. 96-480, at 21; *see also* H.R. Rep. No. 96-1307, pt. 1, at 3. Bayh-Dole thus explicitly replaced the plethora of existing statutory regimes for disposing of patent rights in federally funded research with a "single, uniform national policy." H.R. Rep. No. 96-1307, pt. 1, at 3; 35 U.S.C. § 210(a) (listing the replaced federal statutes). This new, uniform policy allowed "universities and nonprofit organizations," which are "much more efficient in delivering these

important discoveries to the marketplace than are [government] agencies," to "retain patent rights on these discoveries." S. Rep. No. 96-480, at 29. At the same time, the new policy "adequately protect[ed] the legitimate rights of the funding agencies" in the inventions. *Id.* at 30; *see also* 35 U.S.C. § 200 (recognizing the need "to ensure that the Government obtains sufficient rights" in the inventions "to meet the needs of the Government and protect the public").

B. Bayh-Dole has been incredibly successful in accomplishing Congress's purposes. As of the end of FY 2008, 3,381 startup companies formed around university research are still in operation. Press Release, Ass'n of Univ. Tech. Managers, New Survey Reveals Universities' Impact on the U.S. Economy (Feb. 2010). Of those startups, 595 were formed in FY 2008, with 72 percent of the new companies headquartered in the institution's home state. *Ibid.* American universities "create more than two startup companies each working day," and such startups "have longer life spans and raise more capital than non-university affiliated startups." Arundeep S. Pradhan, Op-Ed, *Defending the University Tech Transfer System*, BusinessWeek, Feb. 19, 2010.

Technologies licensed by academic research institutions have spawned new industries such as biotechnology and nanotechnology.[7] "In the period

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[7] Ass'n of Univ. Tech. Managers, Statement on the Role of Federally Funded Univ. Research in the Patent System (2007),

(Continued on following page)

2000-08, U.S. universities received 147,515 invention disclosures, filed 83,988 new patent applications, and signed 41,598 license and option agreements, of which 4,566 were with startup companies based on university research." Pradhan, *supra*. Universities helped bring to market 4,338 new products between 1998 and 2006, or more than 1 new product every day. *The Role of Federally Funded University Research in the Patent System: Hearing Before the S. Comm. on the Judiciary*, 110th Cong. 118 (2007) (statement of Charles F. Louis, Vice Chancellor for Research, University of California, Riverside). Examples of new products arising from university research, include:

- Internet Explorer® (Mosaic) and Eudora Email (U. of Illinois)
- Google® (Stanford)
- Haemophilus B conjugate vaccine (U. of Rochester)
- Osteoporosis treatment (U. of Washington)
- Psoriasis treatment (Harvard)
- LYRICA® for fibromyalgia (Northwestern University)

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http://www.autm.net/AM/Template.cfm?Section=Bayh_Dole_Act&Template=/CM/ContentDisplay.cfm&ContentID=1372.

- TRUSOPT® opthalmic drops used for glaucoma (University of Florida)[8]

Moreover, Bayh-Dole spurs research and innovation beyond the inventions that arise from federal funding. Pursuant to 35 U.S.C. § 202(c)(7)(C), the balance of any patent royalties after expenses and payments to inventors must be used to fund further university research or education. Universities, hospitals, and research institutions received $3.4 billion in patent royalties in 2008, revenue that augments the direct federal investment in research and education.[9]

C. The court of appeals' decision threatens Bayh-Dole's success by undermining the statute's clear and efficient allocation of rights in federally funded inventions. By focusing its analysis, not on the statute, but on dueling contracts that individual researchers might have signed decades ago, the court

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[8] Ass'n of Univ. Tech. Managers, *Technology Transfer Stories: 25 Innovations That Changed the World* 40-42, 94-96, 106-08 (2006); Council on Governmental Relations, *supra*, at 8; Press Release, Ass'n of Univ. Tech. Managers, *supra*; Pradhan, *supra*; Jo Thomas, *Satisfaction in Job Well Done Is Only Reward for E-Mail Software Inventor*, N.Y. Times, Jan. 21, 1997, at A10; Sharita Forrest, *NCSA Web Browser 'Mosaic' Was Catalyst for Internet Growth*, Inside Illinois (Apr. 17, 2003), *available at* http://news.illinois.edu/II/03/0417/index.html; Press Release, Nw. Univ. (Dec. 18, 2007), http://www.northwestern.edu/newscenter/stories/2007/12/lyrica.html.

[9] AAAS Policy Alert (Feb. 25, 2010), http://www.aaas.org/spp/policyalert/policyalert20100225.html.

has created the very confusion and discouragement of development that Congress sought to eliminate.

The court of appeals' decision severely undermines the clarity of title ownership that is essential to incentivizing commercialization. Under the court's analysis, title at any given time could depend on the language of documents signed many years before and of which the university and any prospective industry collaborator are almost certainly unaware. Under such a system a university and its industry collaborator, believing that title rested in the university, could invest in a technology for over 15 years only to face a title challenge at the time of commercialization. *See* GAO Report, *supra*, at 6-7, 10 (recognizing that it can take 10 to 15 years for an invention to reach the market). In this very case, Stanford invested in the subject technology (supported by NIH funds) and worked to protect patent rights in the claimed technology for 20 years before being told in 2009 that those patent rights (as of February 1989) belonged to Roche. Pet. App. 4a, 28a. Such uncertainty of title would, contrary to Bayh-Dole's purpose, discourage private entities from making the investments necessary to bring new products to market. *See* S. Rep. No. 96-480, at 19 (condemning "uncertainties" of patent ownership, which impose "artificial restraints" on commercialization). Indeed, the court of appeals' holding actually creates an incentive for third parties to search for past visitor agreements entered into by university researchers or to entice them to execute new assignments in the

hope of free-riding on the work of universities and their industry collaborators.

By imposing extraordinary burdens on determining patent ownership for federally funded inventions, the court's decision strikes at the heart of the statutory goal of efficient disposition of federally funded patent rights. The court of appeals charged Stanford with constructive or inquiry notice of the assignment in Holodniy's VCA. Pet. App. 16a-17a. Stanford received no actual notice of the purported assignment, which was not recorded in the Patent Office. *Ibid.* Thus, to prevent the loss of patent rights (or identify rights that are lost and truncate further investment), a university's or industry collaborator's lawyers must comb through every possibly relevant document, including seeking documents from any third parties with which the university's researchers might have interacted. Such futile searches would constitute a far worse waste of patent lawyer resources than existed under the regime that Bayh-Dole was intended to correct. *See* S. Rep. No. 96-480, at 30 (condemning the "onerous burden" on government attorneys "trying to determine the ownership of patents arising from the agencies' research and development grants and contracts").

Nor can universities easily remedy the problem through differently drafted faculty employment agreements providing for immediate assignment of any invention. As long as the question of ownership comes down to dueling assignment provisions, as the court of appeals held, universities can never know

whether their own contract will prevail. There can always be another, equally well drafted agreement executed prior to the university's. The only way to avoid the problem of the unknowable engendered by the court of appeals' decision is to make the statutory scheme the ultimate arbiter of interests in federally funded inventions. That is, as demonstrated above, precisely what Congress intended.

III. THE DECISION BELOW SEVERELY IMPAIRS THE FEDERAL GOVERNMENT'S INTERESTS AS WELL AS UNIVERSITIES'

In a footnote, the court of appeals suggested that the federal government (and even Stanford) might have available other remedies by which to vindicate their rights under Bayh-Dole. *See* Pet. App. 20a n.1 (reserving the question "whether the Act provides the Government or Stanford some other legal recourse to recover Holodniy's rights"). But that suggestion flies in the face of the court of appeals' reasoning. Under the logic of its decision, Stanford cannot secure its rights under the Act because the court of appeals has effectively declared that those rights never arose in the first place, having been preempted by Holodniy's assignment to Cetus. The decision's logic will likely also control the resolution of future disputes over *the government's* rights, not just universities', because any suit involving the government's rights would likely be appealed to the Federal Circuit. *See* 28 U.S.C. §§ 1295(a)(1) and (3), 1338(a), 1491, 1498.

The court of appeals' refusal to enforce Stanford's rights under Bayh-Dole necessarily implies that an inventor is free to circumvent the government's rights as well, by assigning ownership to a third party of his choosing. The government, like universities, takes its rights in federally funded inventions only from Bayh-Dole – that statute alone provides the government with the right to deny ownership rights to an inventor or restrict those rights. *See* 35 U.S.C. § 202(d); 37 C.F.R. §§ 401.9, 401.14(a). Thus, the reasoning of the court of appeals' decision precludes the government, as it precludes universities, from asserting its statutory rights in order to protect the public interest in these inventions. *See supra* at 7-9 (discussing the government's march-in and other statutory rights relative to the inventions). For this reason, the court of appeals' footnote purporting to reserve the question of the government's rights is cold comfort to the myriad agencies that might seek to protect their interests in the inventions. *See* Pet. App. 20a n.1.

The court of appeals suggested that the decision in this case was consistent with its earlier decision in *Central Admixture Pharmacy Services, Inc.* v. *Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347 (Fed. Cir. 2007), in which it held that an inventor's violation of the government's rights under Bayh-Dole makes the inventor's rights voidable, but not automatically void. *See id.* at 1352-53. But the court's reliance on *Central Admixture* was misplaced. That decision in fact supports Stanford's position in the present case. In *Central Admixture*, the university

waived its right to retain title and the researcher applied for and received permission, with conditions, from the federal agency to pursue the patent application himself. *Id.* at 1351. The inventor violated a condition of the agency's consent, and the question arose whether the granted request was rendered void or merely voidable at the government's discretion. *Id.* at 1352. The court of appeals recognized that the statute and regulations give the agency discretion whether to take back title in such circumstances. *See* 35 U.S.C. § 202(c)(1)-(3) (agency "*may* receive title to any subject invention" if contractor fails to fulfill obligations) (emphasis added); 35 U.S.C. § 202(d) (if inventor's request is granted, rights are "subject to the provisions of this Act"). *Central Admixture* thus demonstrates the primacy of the statute. In this case, by contrast, Roche does not claim that Holodniy obtained rights pursuant to the statute (he never sought nor received the agency's approval to exercise ownership in the invention). If Holodniy has any rights to which Roche might have succeeded it is because, contrary to the primacy of Bayh-Dole, Holodniy possessed rights independent of any agency approval (or conditions on such approval).

The court of appeals hinted that Stanford and the government might have other remedies, such as suing Holodniy for breach of his contractual obligation to assign his rights in the invention to Stanford. It is far-fetched to think that a suit against an individual inventor, who received not one penny for signing the VCA, could compensate Stanford for

its investment in the invention or the royalties it lost as a result of Holodniy's breach.[10] In any event, the federal government does not contract directly with individual inventors and would have even greater difficulty pressing a breach-of-contract claim against an inventor. Contract damages would not, in any event, be an adequate remedy for the government's loss of its important statutory rights, such as the right to insist that the contractor or inventor make efforts to commercialize the invention and license entities that will manufacture the product in the United States.

The federal government has an important interest in protecting the patent rights of federal funding agencies. Furthermore, the federal government has an important interest in preserving the Congressionally-mandated Bayh-Dole framework, which has served as an incredible engine for economic growth, innovation, and new technologies. *See* GAO Report, *supra*, at 1-2. As demonstrated above, those federal interests are substantially undermined by the court of appeals' decision and warrant this Court's review. If the Court has any question in that regard,

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[10] Although a state law cause of action against the inventor may be available to a university, such as by compelling assignment of a wrongfully obtained patent, *see, e.g.*, *Fenn*, 393 F. Supp. 2d at 141-42, in circumstances like those of this case, such a remedy would be futile as a practical matter. Similarly, assuming state law might provide other theories of relief against Roche, the uncertain outcome of any such litigation itself impairs Bayh-Dole's objectives.

however, *amici* respectfully suggest that the Court invite the views of the United States.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

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April 26, 2010

AMICUS CURIAE BRIEF

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IN THE

Supreme Court of the United States

BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY,
Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., *et al.*,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICUS CURIAE* MASSACHUSETTS INSTITUTE OF TECHNOLOGY IN SUPPORT OF PETITIONER

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STATEMENT OF INTEREST[1]

The Massachusetts Institute of Technology has a direct and immediate interest in how the Bayh-Dole Act, 35 U.S.C. §§ 200-211, affects the clarity of title to federally funded inventions. MIT received $718.2 million in research funding in its 2009 fiscal year. The United States government provided almost 73% of that total ($522.6 million). In addition, the federal government provided $746 million to MIT Lincoln Laboratory, a research and development center that applies advanced technology and rapid prototyping to problems of national security. Since the Bayh-Dole Act became law in 1980, MIT has received an aggregate of $19.9 billion in research funding from the federal government. This enduring flow of research funding to the Institute has produced extraordinary public benefits. A 2009 report concluded that living MIT graduates, faculty, and staff have founded 25,800 active companies, which employ at least 3.3 million people and generate $2 trillion in annual revenue worldwide. If those MIT-

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[1] Pursuant to this Court's Rule 37.2, counsel of record for all parties received notice, at least 10 days prior to the due date, of *amicus's* intention to file this brief. All parties have consented to the filing of this brief, and their letters of consent have been filed with the Clerk of the Court. Pursuant to this Court's Rule 37.6, *amicus* states that no counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amicus* or its counsel made a monetary contribution to the preparation or submission of this brief.

related companies formed a nation, they would comprise the 11th largest economy in the world.[2]

An efficient patent and technology licensing process is a crucial piece of this remarkable innovation system. In fiscal year 2009, MIT was issued 153 new U.S. patents, received 501 new-invention disclosures from its faculty and researchers, filed 131 new U.S. patent applications, and granted 85 patent licenses and options. Twenty-one new companies were formed in 2009 on the basis of MIT licenses. Since 1980, 3,673 U.S. patents have been issued to MIT under the Bayh-Dole Act system. In short, several times every day MIT needs to know, with clarity, who owns this vast array of intellectual property flowing from federal funding.

SUMMARY OF ARGUMENT

The Federal Circuit's decision disregards the language, structure, and underpinnings of the Bayh-Dole Act. The decision threatens a major disruption to the Act's effectiveness. Congress passed the Act in 1980 to promote the commercialization of federally funded inventions and to ensure rights to inventions for the federal government. The Act has served Congress's goals well for three decades.

Before Bayh-Dole, title to federally funded inventions vested in the federal government. Because each funding agency had its own idiosyncratic rules governing invention ownership,

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[2] Edward B. Roberts & Charles Eesley, *Entrepreneurial Impact: The Role of MIT* 8 (Feb. 2009), *available at* http://entrepreneurship.mit.edu/Downloads/Entrepreneurial_Impact_The_Role_of_MIT.pdf.

most inventions were not commercialized or used to their full potential. Bayh-Dole replaced this incentive-frustrating system with a comprehensive system that allows title to federally funded inventions to rest in universities, whose laboratories put billions of federal research dollars to work.

Under the Federal Circuit's decision, title to federally funded inventions is burdened with even greater uncertainty than existed under the pre-Bayh-Dole system. The Federal Circuit decision allows a single researcher, even through sheer inadvertence, to transfer title to a private concern and imperil her or his university's title to the invention, as well as the government's statutorily prescribed right to a license as a return on the federal investment. The private concern can enjoy the benefit of taxpayers' investment in research by using "hereby assign" in its form contract rather than the commonplace "agree to assign" in Stanford's form and those of many other universities. These results turn the statutory scheme on its head. The Federal Circuit erred in failing to consider how Bayh-Dole informs the interpretation of patent assignment language under Federal Circuit law. Had the court properly considered Bayh-Dole, it would have held that the chain of title in this case led to Stanford.

Questions of Bayh-Dole's proper interpretation will arise in cases under the federal patent laws, of which Bayh-Dole is a part. Hence, the Federal Circuit almost certainly will be the only Circuit to decide the question presented. MIT respectfully submits that this Court should grant Stanford's petition now.

ARGUMENT

A. The Bayh-Dole Act Fuels the Innovation Segment of Our National Economy

Over the past 50 years, colleges and universities have become the primary performers of basic research in science and engineering in the United States.[3] In 2007, universities performed 54% of the nation's basic research and 14% of all national R&D.[4] The federal government funds more than half of that university research. Recognizing basic research as a national interest, the federal government invested $32.7 billion in university research in 2008, or 63% of total university research expenditures.[5]

The nation's investment in its research universities has yielded significant economic returns. "Most economic historians agree that the rise of American technological and economic leadership in the [post-World War II] era was based in large part

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[3] David Roessner, et al., *The Economic Impact of Licensed Commercial Inventions originating in University Research, 1996-2007, Final Report to the Biotechnology Industry Organization* 12 (Sept. 3, 2009), *available at* http://www.bio.org/ip/techtransfer/BIO_final_report_9_3_09_rev_2.pdf.

[4] Association of American Universities, *University Research: The Role of Government Funding* 1 (May 2006), *available at* www.aau.edu/WorkArea/DownloadAsset.aspx?id=1122.

[5] Association of University Technology Managers, *AUTM U.S. Licensing Activity Survey: FY 2008* 8 (2008) ("*2008 AUTM Survey*").

on the strength of the American university system."[6] Today, research-intensive American universities dominate the rankings of global higher education,[7] and university research is critical to American industrial competitiveness.[8]

The Bayh-Dole Act plays a central role in this system of innovation. Enacted in 1980 as an amendment to the Patent Act, Bayh-Dole expanded and accelerated the transformation of ideas in the lab into the products, jobs, and revenues of commercial enterprise.

Prior to Bayh-Dole, the federal government's many funding agencies shared no uniform policy for technology transfer. Each agency had its own patent policies, some of which were hostile to universities' holding title to patents. Procedures for allowing universities to manage federal patents were inconsistent and required time-consuming

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[6] Bhaven N. Sampat, *Recent Changes in Patent Policy and the "Privatization" of Knowledge: Causes, Consequences, and Implications for Developing Countries*, in 1 *Knowledge Flows and Knowledge Collectives: Understanding the Role of Science and Technology Policies in Development* 39, 56, *available at* http://unpan1.un.org/intradoc/groups/public/documents/apcity/unpan017425.pdf.

[7] Academic Ranking of World Universities—2009, *available at* http://www.arwu.org/ARWU2009.jsp; Top 200 World Universities, *available at* http://www.timeshighereducation.co.uk/hybrid.asp?typeCode=438.

[8] National Academy of Engineering, *The Impact of Academic Research on Industrial Performance* vii (2003).

negotiation.[9] Relatively few universities operated technology transfer offices,[10] and American universities in total obtained only 250-300 U.S. patents a year.[11] The federal government licensed for commercialization fewer than 5% of the approximately 28,000 patents it held.[12]

Congress recognized that the federal government was investing billions of dollars in cutting-edge research and leaving the vast majority of resulting ideas on the shelf. Congress enacted Bayh-Dole with the express objectives, among others, "to use the patent system to promote the utilization of inventions arising from federally supported research or development[,]" "to promote collaboration between commercial concerns and nonprofit organizations, including universities[,]" and "to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions[.]" 35 U.S.C. § 200.

Bayh-Dole aimed to achieve its stated ends with a simple but profound reversal of assumptions. Rather than the federal government holding patents under numerous conflicting policies, universities now hold

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[9] BayhDole25, Inc., *The Bayh-Dole Act at 25* 2 (Apr. 2006), *available at* http://www.bayhdole25.org/sites/bayhdole25.org/files/BayhDole25_WhitePaper_20060417.pdf.

[10] *2008 AUTM Survey*, *supra* note 5, at 13.

[11] David C. Mowery, et al., *Ivory Tower and Industrial Innovation: University-Industry Technology Transfer Before and After the Bayh-Dole Act* 133 (2004).

[12] Homer A. Neal, et al., *Beyond* Sputnik*: U.S. Science Policy in the 21st Century* 106 (2008).

patents under a single, comprehensive legislative system.[13] *Id.* § 202(a).

The resulting change in technology transfer has been dramatic. The number of university technology licensing offices has grown into the hundreds.[14] As summarized in the following figure, the number of U.S. patents issued to universities has grown dramatically since the passage of Bayh-Dole, to reach into the thousands each year:

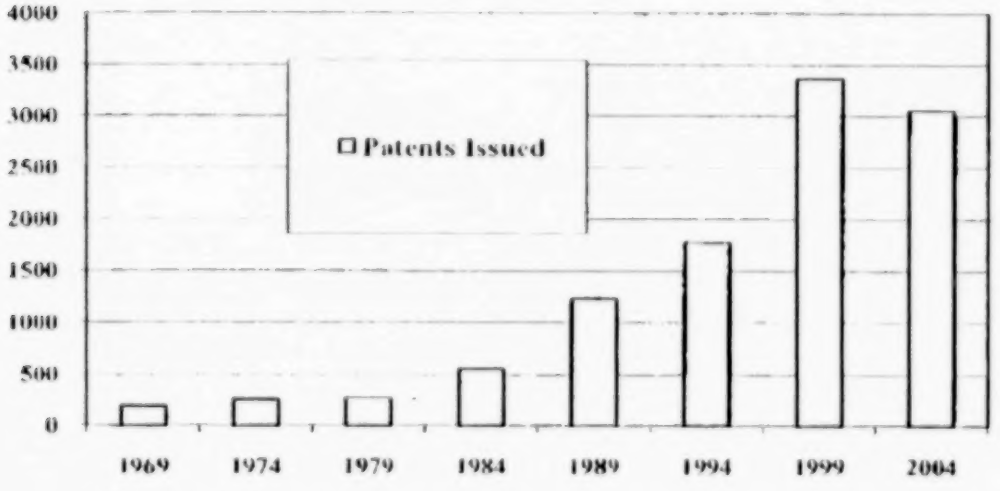

Figure 1: Number of U.S. Patents issued to U.S. Universities, 1969-2004.[15]

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[13] Jonathan R. Cole, *The Great American University: Its Rise to Preeminence, Its Indispensable National Role, Why It Must Be Protected* 163 (2009).

[14] *2008 AUTM Survey*, *supra* note 5, at 13.

[15] David C. Mowery, et al., "The growth of patenting and licensing by U.S. universities: an assessment of the effects of the Bayh-Dole act of 1980," 30 *Research Policy* 99, 104 (2001); United States Patent & Trademark Office, *U.S. Colleges and Universities Utility Patent Grants 1969-2005*, http://www.uspto.gov/web/offices/ac/ido/oeip/taf/univ/asgn/table_1_2005.htm.

In every year since 1995, universities have obtained 10 times more patents than they did in a typical year before 1980. Universities received approximately 1.5% of all U.S. patents issued in 1981 and over 5% in 2008, when universities received 3,280 patents.[16]

This increase in patenting and exploitation of federally funded inventions is not the result of happenstance. It is a direct consequence of the tradeoff between title and use that Bayh-Dole mandates. In return for allowing universities to retain title to inventions conceived or implemented with federal dollars, Congress requires universities to comply with substantive requirements that further Congress's stated objectives. The Act requires, *inter alia*, disclosure and diligent patenting of inventions; the licensing and exploitation of the rights to those inventions; the payment of royalties to inventors and reinvestment in further research; and the government receiving a paid-up license to practice the invention. *See* 35 U.S.C. § 202(c).

The results under Bayh-Dole speak to the statute's effectiveness at achieving its aims. In 1991, universities executed 1,229 new patent licenses and patent-license options—a sharp increase over the typical number before 1980.[17] That number has more than quadrupled again since 1991 to 5,132 in 2008.[18]

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[16] Cole, *supra* note 13, at 166; *2008 AUTM Survey*, *supra* note 5, at 9.

[17] *The Bayh-Dole Act at 25*, *supra* note 9, at 23.

[18] *2008 AUTM Survey*, *supra* note 5, at 9.

Critically important economic activity flows from these university licenses. As illustrated below, a 2008 study estimates that the sale of products based on university-licensed patents contributed, in aggregate, between $47.4 *billion* and $186.6 *billion* to the U.S. gross domestic product between 1996 and 2007 (the variance within this range depends upon assumptions about royalty rates).[19]

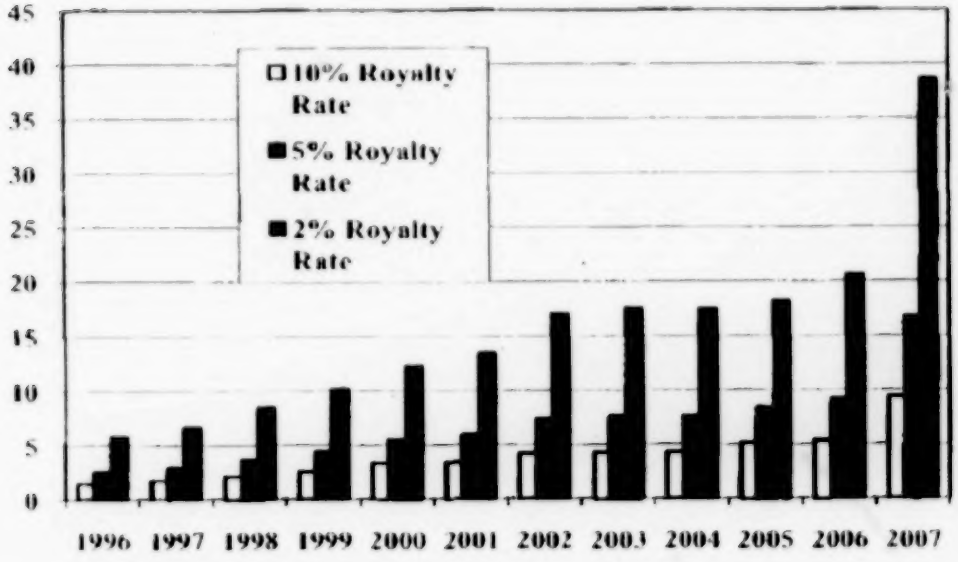

Figure 2: Annual Change in U.S. G.D.P. due to University-Licensed Products, Selected Royalty Rates, 1996-2007 (in billions of dollars).[20]

In addition to generating sales revenue, patent licenses also lead to necessary investments in pre-product technology development. An MIT study in 1995 estimated that its 205 then-active, exclusive

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[19] Roessner, *supra* note 3, at 32-33.

[20] *Id.* at 33. (The large increase in 2007 was due primarily to one university's sale of a patent interest.)

licenses had induced $922 million in investments in pre-production development. Extrapolating those results to all research universities' then-active, exclusive licenses, the study estimated that university licenses resulted in pre-production investments between $2.5 billion and $5 billion in 1993, with the creation of between 20,000 and 40,000 jobs.[21]

Many university licensees are newly created start-up companies. From 1980 through 2006, 5,724 new companies have been created as a result of universities licensing federally funded inventions.[22] Start ups and other small businesses are a primary engine for new job creation. One study estimated that over the 12-year period 1996 through 2007, university-licensed inventions and products have created more than 279,000 jobs.[23]

In enacting Bayh-Dole, Congress intended to achieve exactly this alignment of incentives as well as the resulting positive economic effects. As one of the Act's sponsoring Senators recently explained:

> Bayh-Dole recognizes that the idea alone has no value. [The Act] is designed to create the incentive for

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[21] Lori Pressman, et al., "Pre-Production Investment and Jobs Induced by MIT Exclusive Patent Licenses: A Preliminary Model to Measure the Economic Impact of University Licensing", VII *Journal of the Association of University Technology Managers* 28, 37, 44-45 (1995).

[22] Association of University Technology Managers, *AUTM U.S. Licensing Survey: FY 2006* 5 (2006).

[23] Roessner, *supra* note 3, at 34-35.

> entrepreneurs to invest in the idea and provide the development capital necessary to create a valuable product out of the idea. The marriage of intellectual property and its developmental partner is the basis of Bayh-Dole's success.[24]

A 2001 report by the National Institutes of Health to Congress likewise described the substantial benefits that the Bayh-Dole system has created: "Current practices in technology transfer have yielded a dramatic return to the taxpayer through the discovery of new technologies that extend life and improve the quality of life and through the development of products that, without the successful public-private relationship, might not be available."[25]

Finally, and perhaps most significant of all, federally funded university research, patented and licensed through the Bayh-Dole patent system, and amplified by nonfederal, venture capital investment, continuously re-invents yesterday into a surprising, exciting, and enriched tomorrow. Needless to say, inventions were conceived in university laboratories long before Bayh-Dole. But the Act exerts powerful leverage in the technology transfer system, and that system fuels innovation that is essential to the nation's competitive edge in science and technology and its economic well-being.

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[24] Senator Birch Bayh, "Bayh-Dole: Don't Turn Back the Clock," 41 *les Nouvelles* 215, 217 (Dec. 2006).

[25] Association of University Technology Managers, *AUTM Licensing Survey: FY 2000* 2d Introductory Page (2000).

B. The Bayh-Dole Act System Rests Upon Clarity of Title to Federally Funded Inventions—A Clarity that the Federal Circuit Opinion Undermines

The Federal Circuit's decision threatens to undermine the landmark and proven achievements of Bayh-Dole, and to replace them with a chaotic patchwork of uncertainty as to who owns federally funded inventions. In particular, the Federal Circuit failed to consider Bayh-Dole's relevance to the chain of title to the underlying inventions. Had the court considered the import of the Bayh-Dole Act to the federal question of patent assignments, the court would have found that the chain of title led to Stanford and stopped there.

As demonstrated, Bayh-Dole by design replaced an uncertain system of ownership of inventions conceived or first reduced to practice under a federal funding agreement—what the Act calls "subject inventions"—with a clear sequence of ownership rights. In particular, the Act provides that universities and other defined parties who contract with the federal government to conduct research may "*elect to retain title* to any subject invention[,]" provided they comply with the Act's substantive requirements for disclosure, licensing, and the payment of royalties to inventors. 35 U.S.C. § 202(a)-(c) (emphasis added). Significantly, the Act provides that, if the university does *not* elect to retain title, then the determination whether the underlying inventor may retain rights to the underlying invention rests with the relevant federal agency, in consultation with the university or other contractor:

> *If a contractor does not elect to retain title to a subject invention* in cases subject to this section, the Federal agency may consider and after consultation with the contractor grant requests for retention of rights by the inventor subject to the provisions of this Act and regulations promulgated hereunder.

Id. § 202(d) (emphasis added).

Section 202(d), and indeed the entire Act, are premised on universities and other contractors obtaining title to subject inventions from researchers and others who perform the underlying research. Otherwise Bayh-Dole makes no sense in giving a university the right to "elect to retain title to any subject invention[,]" *id.* § 202(a), or, conversely, the right "not [to] elect to retain title to a subject invention in cases subject to" the Act. *Id.* § 202(d).

The Act further assumes that the university will hold title by requiring that any funding agreement between the university and the government contain "a prohibition upon the assignment of rights to a subject invention in the United States without the approval of a Federal agency[.]" *Id.* § 202(c)(7)(A). That prohibition necessarily assumes that the university in the ordinary course obtains and retains title. Likewise, section 203, which sets forth the federal government's "march-in rights" concerning subject inventions, speaks of "any subject invention in which a small business firm or nonprofit organization *has acquired title under this chapter*[.]" *Id.* § 203(a) (emphasis added). And the final clause of section 202(d), quoted above, makes clear that

even if the federal agency, in consultation with the university, decides that an inventor will retain rights to the underlying invention, the inventor's exercise of those rights is "subject to the provisions of this Act and regulations promulgated hereunder." *Id.* § 202(d). If the Act assumed that the inventor had title to subject inventions, then the restriction on the inventor's exercise of retained rights would be a non sequitur; an inventor who had title in the first instance would be able to exercise those rights free and clear of any obligation to comply with Bayh-Dole or implementing regulations. But that is not what the Act provides.

The Federal Circuit's decision in this case disregarded all of Bayh-Dole's structural underpinnings. In particular, the Federal Circuit erroneously concluded that Bayh-Dole was relevant only at the time Stanford, in 1995, made its election to retain title to the underlying subject invention. The Federal Circuit framed the Bayh-Dole inquiry as whether the Act in 1995 "automatically void[ed] the patent rights that Cetus received from Holodniy [one of the inventors]" in 1989; the court concluded that the Act did not void that purported receipt of title by Cetus. Pet. App. 21a.

The Federal Circuit erred in failing to recognize that Bayh-Dole was relevant to answering the critical *antecedent* question of federal law in the case: whether Holodniy had patent rights to convey to Cetus in 1989.[26] Before Holodniy ever visited Cetus,

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[26] The Federal Circuit expressly held that "the question of whether contractual language effects a present assignment of patent rights, or an agreement to assign rights in the future," is a federal question implicating the Patent Act. Pet. App. 12a.

he had executed the Copyright and Patent Agreement in favor of Stanford (the "CPA"). *Id.* 118a. Holodniy expressly recognized in the CPA that Stanford "enters into agreements ('Contracts or Grants') with third parties including the United States Federal Government ('Sponsors')"; he agreed to disclose "any invention (whether or not it may be considered patentable) under or in the course of a[] Contract or Grant"; and he further "agree[d] to assign or confirm in writing to Stanford and/or Sponsors that right, title and interest in and to ... such inventions as required by Contracts or Grants[.]" *Id.* 118a-119a. The obvious purpose of the CPA was to ensure both the disclosure of, and Stanford's acquisition of title to, any subject invention created under a federal grant. It is thus clear that the CPA was designed to allow Stanford to comply with the substantive provisions of Bayh-Dole. *See* 35 U.S.C. § 202(a)-(c).

The Federal Circuit, however, failed to consider the effect of Bayh-Dole on the rights that Stanford obtained to any subject invention through the CPA. The court instead resolved that question by relying on cases that did not involve Bayh-Dole and that did not involve competing claims of ownership by assignees with "agree to assign" and "hereby assign" clauses in their assignment agreements. Those cases concerned whether an assignee had legal title so as to be able to sue on assigned patent rights. Pet. App. 13a-14a. Stanford's use of the language, "I agree to assign" in the CPA, *id.* 119a, is commonplace form

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The Bayh-Dole Act, codified at 35 U.S.C. §§ 200-211, of course is now part of the Patent Act.

language that reflects the fact that, at the time an individual begins her or his research work at a university, she or he has no invention to assign.

The Federal Circuit did not consider at all whether its formalistic reliance on the inapposite distinction between "agree to assign" and "hereby assign" does violence to the language, structure, and objectives of Bayh-Dole. The Act presumes that universities obtain title to subject inventions that their researchers invent under federal grants. By disregarding the impact on Bayh-Dole's structural scheme, the Federal Circuit has created tremendous uncertainty regarding the question of title in the case of any university that has used "agree to assign" language in its invention agreements, as well as any university whose researchers and employees working on federally funded grants have visited private research facilities in the course of their work. This result runs directly counter to the clarity of title, and increased commercial exploitation of inventions, that Congress sought to ensure through Bayh-Dole.

The transfer of ownership, even inadvertently, of federally funded inventions from universities to private entities directly undermines Congress's substantive goals. Universities, in exchange for the retention of title, must comply with the Act's substantive requirements, which, as described, are designed to and do further Congress's objectives in the Act. *See* 35 U.S.C. § 202. Private entities that do not receive federal funding are not subject to those requirements. Bayh-Dole also requires that, where the contractor elects rights, the relevant "[f]ederal agency shall have a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have

practiced for or on behalf of the United States any subject invention throughout the world[.]" 35 U.S.C. § 202(c)(4). Where a single researcher who has "agreed to assign" inventions to a nonprofit university, as Bayh-Dole envisions, instead "hereby assigns" purported rights in those inventions to private commercial laboratories, the Federal Circuit's decision literally means that this statutorily prescribed return on the federal government's investment is nullified to the advantage of a private business. These results are contrary to Bayh-Dole's purpose and undermine the overall statutory scheme.

In sum, the Federal Circuit erred by evaluating the assignment issue in a vacuum, without proper consideration of Bayh-Dole's relevance to this question of federal law. The court should have concluded, in light of the text, structure, and purpose of Bayh-Dole, that the Federal Circuit law on contractual assignments of patents results in the chain of title leading to Stanford and subject to Bayh-Dole. Because the Federal Circuit erred in its interpretation of this important federal statute in this critical context, the Court should grant certiorari.

Because the question is one of surpassing national importance; because the Federal Circuit significantly erred and in doing so undermined the purpose and effectiveness of Bayh-Dole; and because the question will not benefit from further percolation in the federal courts, *amicus* respectfully submits that the Court should grant certiorari now. At a minimum, *amicus* respectfully suggests that the Court should ask for the views of the United States,

which has a critical interest under Bayh-Dole in the resolution of this question.

CONCLUSION

Stanford's petition for a writ of certiorari should be granted.

April 26, 2010

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AMICUS CURIAE BRIEF

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IN THE

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BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,
Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., ROCHE DIAGNOSTICS CORPORATION, and ROCHE DIAGNOSTICS OPERATIONS, INC.,
Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICI CURIAE* WISCONSIN ALUMNI RESEARCH FOUNDATION ET AL. IN SUPPORT OF STANFORD'S PETITION FOR CERTIORARI

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STATEMENT OF INTEREST*

Amici have no interest in the patents-in-suit or the outcome of this particular lawsuit. *Amici* are, however, gravely concerned that the Federal Circuit's decision will cloud universities' title to thousands of federally funded inventions, contrary to Congress's intent and the public interest.

At stake here is who owns the rights to the inventions generated by the tens of billions of dollars that Congress annually appropriates to support academic research. Those funds enable critical research in many fields, including medicine, biotechnology, applied mathematics, and electrical engineering. The resulting inventions have charted new approaches to critical problems, founded entire industries, and improved millions of lives throughout the world. In the health field, for example, fortifying foods with vitamin D helped eradicate rickets, the blood thinner Coumadin® has enabled patients to avoid and survive strokes and heart disease, and magnetic resonance imaging (MRI) has made it easier to diagnose and treat many ailments.

Owning inventions enables universities to enjoy returns if those inventions are commercialized, and royalties from licenses have contributed significantly to universities' research and educational missions.

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* All parties have consented to the filing of this brief. No party or counsel for a party authored any portion of this brief or made a monetary contribution intended to fund its preparation or submission. No one other than *amici*, their members, and their counsel have made such a monetary contribution. *Amici* notified respondents' counsel of their intention to file this brief more than 10 days before its due date.

But *amici*'s interest goes far beyond that. As shown below, the Bayh-Dole Act of 1980 granted universities and other nonprofit research institutions initial title to federally funded inventions in order to promote the transfer and commercialization of federally funded research for the benefit of the public.

SUMMARY OF ARGUMENT

The Federal Circuit's decision is wrong and, if not reversed, will return the world to the pre-1980 era when uncertainty over ownership of federally funded inventions impeded their transfer and commercialization. If, as the Federal Circuit has held, individual researchers initially own federally funded inventions and may unilaterally transfer their interests to third parties, the Bayh-Dole Act will have been negated and decades of public benefits from transfer of university-developed research will be in jeopardy.

Review should be granted now and should not be deferred until another case. The effects of the decision below will be vast and immediate. The Bayh-Dole Act was designed to clarify title to federally funded inventions. With this decision, the Federal Circuit has clouded the title to a host of inventions, inevitably discouraging licensing and commercialization as well as spawning needless litigation. Because the Federal Circuit has nationwide jurisdiction, the effect will be nationwide and a split in the circuits is unlikely to develop.

At a minimum, the Court should call for the views of the Solicitor General so that the federal government can confirm the errors in the court of appeals' construction of the statute and the importance of the issues to both the government and the nation.

ARGUMENT

A. The Court of Appeals Misunderstood and Misconstrued the Bayh-Dole Act

This case turns on the Bayh-Dole Act, 35 U.S.C. §§ 200 et seq., and its effect on who owns rights in inventions made with federal funding. The Federal Circuit held that an individual inventor (Holodniy) owned initial title to a portion of an invention that he and other Stanford employees jointly made using federal funding, and that the inventor could and did transfer those rights to a private company (Cetus, predecessor to Roche) because neither the funding agency (NIH) nor the contracting research institution (Stanford) had claimed patent rights previously. Pet. App. 18a–21a. Although the Federal Circuit recognized that Stanford disclosed the invention and claimed title within the statutory time period, the court held that "claiming title under Bayh-Dole does not override prior assignments." *Id.* at 21a.

The Federal Circuit fundamentally misunderstood the Bayh-Dole Act. As shown below, the statute is clear: title to federally funded inventions originally vests in the contracting *research institution*, not the inventor or third-party collaborators. In this case, Stanford timely disclosed the invention to the funding federal agency and timely elected to retain its statutory ownership rights. Holodniy had no rights to assign to Cetus, and Stanford had standing to sue Roche for infringement.

Before 1980, the federal government—not individual inventors and not contracting research institutions—owned default rights to inventions made using federal research funds. Different agencies had

different policies about transferring those rights, and the resulting lack of clarity and conformity hampered commercialization of federally funded research. *See* S. Rep. No. 96–480, 96th Cong., 1st Sess. 2–3 (1979) ("Senate Report") (noting dozens of conflicting agency policies and that only 4% of federal patents had been successfully licensed; concluding that "ineffective patent policies regarding ownership of potentially important discoveries" were preventing "deliver[y of] new inventions and processes from [federal] research and development programs to the marketplace where they can benefit the public").

The Bayh-Dole Act, adopted in 1980, changed the landscape by clearly vesting ownership of inventions made in whole or in part with federal funds in the contracting institutions. Individual inventors are entitled to a share of any royalties, but they cannot own title to the invention unless the institution waives title and the government agency consents.

Inventions subject to the Act include "any invention of the contractor conceived or first actually reduced to practice in the performance of work under a [federal] funding agreement," such as a grant. 35 U.S.C. § 201(e). Under section 202(a), ownership rights to all such "subject inventions" are allocated to contracting research institutions if those institutions elect to "retain title" to them:

> Each nonprofit organization or small business firm may, within a reasonable time after disclosure as required by paragraph (c)(1) of this section, elect to retain title to any subject invention ....

35 U.S.C. § 202(a).[1]

Section 202(a) nowhere states or suggests that individual inventors own initial title or can defeat the contracting research institution's right to retain title. The statute provides that the research institution may waive title by not disclosing the invention, by not electing in writing to retain title to it, or by not filing a timely patent application. *See* 35 U.S.C. § 202(c). Moreover, the statute gives the federal government certain license and "march-in" rights and limits assignments. *See* 35 U.S.C. §§ 202(c), 203(a), 204. But the institution's title is not subject to rights or claims of individual inventors.

Other provisions of the Bayh-Dole Act confirm that research institutions own original title to the fruits of their federally funded research and that individual inventors have only contingent, secondary rights if the institution waives its ownership rights. Under 35 U.S.C. § 202(d), individual inventors may claim patent rights *only* if the contracting institution does not elect to retain title *and* the funding agency then consults with the institution and grants the inventor's request:

> If a contractor does not elect to retain title to a subject invention in cases subject to this section, the Federal agency may consider and after consultation with the contractor grant requests for retention of rights by the inventor subject to the provi-

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[1] Section 202(a) contains a proviso allowing a federal agency to specify otherwise in a particular funding agreement if one of four specific circumstances applies. Those circumstances are rare, however, and irrelevant to this case.

> sions of this Act and regulations promulgated hereunder.

Moreover, under 35 U.S.C. § 202(c)(7)(B), institutions are to "share royalties with the inventor," confirming that the basic right to royalties belongs to the institutions. *See also* 35 U.S.C. § 202(c)(7)(C) (contractor expected to use royalties remaining after expenses, including such payments to inventors, for the support of scientific research or education).

Furthermore, Congress dictated that funding agencies must approve all assignments of rights in inventions made under contracts with nonprofit organizations such as Stanford, thereby setting a high bar to assumption of ownership by others. *See* 35 U.S.C. § 202(c)(7)(A) (excepting only assignments to invention management organizations). The governing regulations confirm that "the ownership provisions ... remain applicable in any invention 'conceived or first actually reduced to practice in performance' of the project," regardless of whether other sources provided supplemental research funding. 37 C.F.R. § 401.1. The statutory limits on assignments would be pointless if, as the Federal Circuit has held, individual inventors owned initial title and could freely assign away their ownership rights through side agreements that neither the research institution nor the funding agency has reviewed and approved.

Finally, the legislative history of the Bayh-Dole Act confirms that it was intended to grant initial title to contracting research institutions, not individual inventors. The Senate Report accompanying the Act noted that "Section 202 establishes the basic framework for the disposition of rights in [federally

funded] inventions" and that "Section 202(a) provides that as a normal rule small business firms and nonprofit organizations are to have the *right to elect to retain worldwide ownership* of their inventions by making an election within a reasonable time after they disclose the invention." Senate Report at 31 (emphasis added); *see also id.* at 29 (bill would "allow [university and nonprofit] contractors to retain patent rights on these discoveries while allowing the funding agencies to have free access to them"). Later, the Senate Report included findings of the Congressional Budget Office, which summarized the bill as "*automatically grant[ing] small businesses and nonprofits title* to inventions arising from Government-supported research unless the contracting agency could justify, through specified procedures, holding title to the invention." *Id.* at 36 (emphasis added).

In short, initial patent rights in federally funded research belong to the funded contractors. Individual researchers and third parties may not bypass that allocation unilaterally. That principle is clear from both the text of the statute and its legislative history, and that principle was understood and accepted in the research community until this case.[2]

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[2] Contrary to the Federal Circuit's suggestion, *Central Admixture Pharmacy Services, Inc. v. Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347, 1352–53 (Fed. Cir. 2007), merely recognized that a party may waive title to an invention. The court stated that "title remains with the named inventors or their assignees" until the government chooses to void it for non-compliance with the Act. *Id.* But the reference to "named inventors" reflected the unusual facts: the researcher there obtained title after (1) the university had abandoned the invention and (2) the funding agency had granted his request for title under 35 U.S.C. § 202(d). *Id.* at

B. Ownership of Patent Rights to Federally Funded Inventions Is a Question of Great Importance

The Bayh-Dole Act is vitally important to our economy. Indeed, the *Economist* once called it "[p]ossibly the most inspired piece of legislation to be enacted in America over the past half-century," one that "helped to reverse America's precipitous slide into industrial irrelevance." *Innovation's Golden Goose*, THE ECONOMIST (Dec. 12, 2002).

Federal agencies such as the National Institutes of Health, the National Science Foundation, and the Office of Naval Research sponsor much of the research performed at universities today. Before Bayh-

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1351. The court nowhere suggested that title had not vested initially with the university.

University of Pittsburgh v. Townsend, No. 3:04–CV–291, 2007 WL 2263079 (E.D. Tenn. Aug. 3, 2007), *aff'd*, 542 F.3d 513 (6th Cir. 2008), also cited by the Federal Circuit, also sheds no light. It was an unpublished trial court decision that addressed a different issue (the statute of limitations) and cursorily distinguished the district court's decision in this case on a variety of grounds. The court did not analyze the Bayh-Dole Act.

Finally, *Fenn v. Yale University*, 393 F. Supp. 2d 133 (D. Conn. 2004), dealt with whether the Bayh-Dole Act preempted a university's state law tort counterclaims against a former faculty member. In passing, the court observed that the Act's "primary purpose" was "to regulate relationships of small business and nonprofit grantees with the Government, not between grantees and the inventors who work for them." *Id.* at 141–42. The point, however, was that the Act was not designed to benefit individual researchers and thus did not preempt institutions' claims against them.

Dole, title to the inventive fruits of that research was often unclear and subject to the vagaries of agency policies. When title was clear, it was often held by funding agencies that were ineffective at licensing the inventions and fostering their commercialization. *See* Senate Report at 2–3.

By granting research institutions clear initial title to federally funded inventions, Congress encouraged licensing and commercialization of those inventions. The result was a boom in the transfer of the results of federally supported research through patenting and licensing by universities, the establishment of technology transfer offices at many institutions, and the development of public-private partnerships around the country.[3] University-owned inventions have become a major engine of economic growth. Indeed, a recent report estimates that university licensing contributed between $108.5 and $457.1 *billion* to the U.S. economy from 1996 to 2007.[4] In contrast, little licensing of federally funded inventions occurred before 1980. Senate Report at 2.

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[3] *See generally* David Roessner et al., *The Economic Impact of Licensed Commercialized Inventions Originating in University Research, 1996–2007: Final Report to the Biotechnology Industry Organization* (Sept. 3, 2009) ("BIO Report"); Howard Bremer et al., *The Bayh-Dole Act and Revisionism Redux*, 78 PAT., TRADEMARK & COPYRIGHT J. 483 (Aug. 14, 2009). "[G]rowth during the 1970s in patenting, licensing, licensing income, or in the establishment of independent technology transfer offices, was dwarfed by the surge in all of these activities after 1981." BIO Report, *supra*, at 18 (citing David C. Mowery, *The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act of 1980*, 30 RES. POL'Y 99, 104 (2001)).

[4] BIO Report, *supra* note 3, at 34.

The Federal Circuit's opinion threatens to undermine these advances. The success of the Bayh-Dole Act stems from its carefully crafted and balanced statutory scheme: universities and other research institutions receive ownership of federally funded inventions in exchange for a commitment to use their best efforts to commercialize the inventions for the benefit of the public. The fundamental premise of the statute—that clarifying who owns and can license federally funded inventions will encourage their development and exploitation—is now in jeopardy.

Simply put, the Federal Circuit's opinion eliminates the certainty of title that has been the cornerstone of university-industry relationships under the Bayh-Dole Act for nearly 30 years. Until this case, research institutions and corporations alike understood that title to federally funded inventions belongs to the contracting institution unless the institution has disclaimed ownership or failed to follow the terms of the statute. Indeed, "[t]he most significant feature of the Act was that it changed the presumption of title to any invention made ... through the use, in whole or in part, of government funds from the government to the contractor-grantee."[5] Under the court of appeals' decision, that presumption of title has disappeared: title may belong to individual inventors or to whomever those inventors may have assigned it (advertently or inadvertently).

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[5] Howard Bremer, *University Technology Transfer: Evolution and Revolution*, in COUNCIL ON GOVERNMENTAL RELATIONS, 50TH ANNIVERSARY J. OF PAPERS 13, 20 (1998).

The practical problems that will result from the Federal Circuit's misreading of the Bayh-Dole Act are obvious. Consider a case involving four university employees working on federally funded biotechnology research. One visits the laboratory of a private company and signs an access/confidentiality agreement addressing invention rights. The second acquires research equipment from another company and signs a form purporting to assign ownership of any inventions conceived or made through the use of the equipment to that company. The third obtains supplemental research funding under a contract with a third company that also addresses intellectual property rights. The fourth assigns any intellectual property rights that she may own to a start-up company in which she holds equity.[6]

Under the Federal Circuit's opinion, it will be virtually impossible to know who has what rights to exploit the invention because any of the inventors' agreements could override the Bayh-Dole Act's assignment of ownership to the university. If a valuable invention were developed, the result would be a battle of the forms, with lawyers parsing contracts to determine who transferred what rights and whether such assignments technically occurred before or after the employees assigned ownership to the university under the terms of their employment contracts. Alternatively, and more likely, nothing valuable would be developed because everyone would conclude that title to the invention was too uncertain or too

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[6] This hypothetical may seem extreme, but it is nonetheless representative. Most universities now encourage faculty members to consult with the private sector, and such collaborations are beneficial for society as a whole.

splintered to justify investing in refining and commercializing the invention. The Bayh-Dole Act was designed to prevent that result.

In fact, this hypothetical is optimistic because it assumes full information. Historically, a company wanting a license understood that it needed to contract with the university that received the federal funds. The university and industry could rest assured that no side deals or unknown agreements would affect the rights negotiated. For example, an exclusive licensee knew that it was the only private party with rights to exploit the invention. Under the decision below, however, neither the university nor its licensee can know whether a third party will claim a license or superior ownership rights based on some obscure agreement that neither knew existed. Again, the result would be the uncertainty and concomitant disincentives for university-industry partnerships that Congress aimed to avoid.

In short, "[t]he certainty of title in the universities to inventions made with government funds afforded by the Bayh-Dole Act ... provided the major impetus to new and expanding university-industry relationships."[7] The Federal Circuit's decision would destroy that certainty and roll back decades of progress. Equally troubling, the court of appeals' reading would allow private companies to gain the benefits of federal funds (in effect a taxpayer subsidy), yet avoid the conditions that the Act imposes on research institutions in the public's interest.

It is no answer to suggest that universities can avoid such results by policing employees and forbid-

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[7] H. Bremer, *supra* note 5, at 21.

ding them from signing agreements assigning patent rights. Even if faculty remembered the edict in their haste to pursue research, most are not intellectual property experts. It is impractical and impracticable to expect them to understand nuances of legalese.

This case is a good example. Signing a visitor's confidentiality agreement does not obviously implicate the legal rights between a researcher and his or her university, much less the university's ability to obtain and license a patent on resulting inventions. Moreover, requiring universities to police faculty-industry partnerships would drain scarce resources, and effective policing would inevitably inhibit or at least delay fruitful collaborations. Nothing in the legislative history suggests that Congress intended such inefficient transaction costs, or that unauthorized acts by researchers would undermine invention management by universities.

Nor is it any answer to say that universities should simply draft employment agreements that presently convey rights rather than terms requiring faculty members to execute assignments after each invention is made. To begin with, that would still leave decades of inventions whose ownership would remain clouded by the panel opinion. As Stanford notes (Pet. 17–18), many universities' standard faculty employment contracts contain "agree to assign" language. In any event, except as trumped by federal laws such as the Bayh-Dole Act, patent ownership is a matter of state law. No one knows for sure whether the courts would uphold the enforceability of mandatory employment contracts that purport to assign ownership of inventions that do not exist at the time. Universities may face a Catch-22.

Finally, apart from its economic consequences, the panel opinion threatens academic freedom. When universities license their patent rights, they ordinarily preserve the right to conduct further research. Under the decision in this case, however, a company may entice a researcher to assign away ownership rights, obtain a patent, and then dictate whether that researcher—or anyone else—may continue to conduct research in the field. That is so because the Federal Circuit has narrowly construed the "experimental use" exception to patent infringement, reasoning that "research projects with arguably no commercial application whatsoever" can infringe merely because they "educat[e] and enlighten[] students and faculty" and "increase the status of the institution." *Madey v. Duke Univ.*, 307 F.3d 1351, 1362 (Fed. Cir. 2002). The specter of interference with academic research is yet another reason why this Court should ensure that title to federally funded inventions belongs initially to research institutions and not to individual researchers.

C. Review Needs to Be Granted Now and Cannot Await Another Case

The Court may be tempted to wait and see how the consequences of the decision play out. *Amici* urge the Court not to do so.

To begin with, this case presents an appropriate vehicle to decide the question presented. The legal issue is squarely and starkly presented, and the judgment is final.

Second, delay will only cause the damage to mount. The effects of the Federal Circuit's decision have been great and immediate. As discussed above,

the Bayh-Dole Act was designed to clarify research institutions' title to federally funded inventions. This decision now re-clouds the title to thousands of patents, many of which have already been licensed and commercialized. More litigation over ownership of existing patents and standing to sue on them will inevitably result.[8] Worse, doubts about universities' title to current and future patents will dissuade licensees and investors, inhibiting the technology transfer and university-industry partnerships that Congress strove to promote. The effects will be doubly pernicious because those effects will be largely invisible: when title is uncertain, transactions simply will not happen.

Finally, further "percolation" in the lower courts will be minimal. Litigation will normally arise in conjunction with patent lawsuits, and the Federal Circuit has exclusive and nationwide jurisdiction over all actions arising under all statutes relating to patents. *See* 28 U.S.C. §§ 1295(a)(1), 1338(a). The Federal Circuit has denied rehearing *en banc*, and it is unlikely to change its mind in the near future.

There is no reason to wait.

D. The Court Should at Least Call for the Views of the Solicitor General

For the reasons discussed above, *amici* submit that this Court should grant certiorari and reverse without further ado. Nevertheless, if the Court has any doubt about whether review is warranted, *amici*

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[8] Litigation over ownership of federally funded inventions was rare before this case because research institutions' ownership rights were so well recognized.

urge the Court to call for the views of the Solicitor General, who can confirm the legal errors and practical consequences of the decision below, including the consequences for the federal government itself.

The federal government has an obvious and substantial interest in who owns the rights to exploit federally funded inventions. Federal agencies spend tens of billions of dollars each year supporting academic research.[9] Moreover, the Bayh-Dole Act itself confirms the federal interest in ensuring that inventions enabled by federal funds inure to the public good. *See* 35 U.S.C. § 200 (stating Congress's policies and objectives).

Furthermore, although the court of appeals purported not to decide whether an individual inventor's assignment may override the government's rights under the Bayh-Dole Act (*see* Pet. App. 20a n.1), there is no basis to distinguish between the statutory rights of agencies and research institutions. For example, if an individual inventor holds initial title in a federally funded invention and assigns away his or her rights, leaving the research institution with no title, then the federal government likewise will have no paid-up license under 35 U.S.C. § 202(c)(4), no march-in rights under 35 U.S.C. § 203(a), and so forth. The Court should at least consult the Solicitor General before countenancing that dangerous result.

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[9] *See* National Science Board, SCIENCE AND ENGINEERING INDICATORS 2010, at 5-9 & appendix table 5-2, *available at* http://www.nsf.gov/statistics/seind10/ (reporting that the federal government "accounted for about 60% of the $51.9 billion of R&D funds expended by universities and colleges in FY 2008").

CONCLUSION

Stanford's petition for a writ of certiorari should be granted. At a minimum, the Court should call for the views of the Solicitor General.

Respectfully submitted,

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April 23, 2010

JOINT APPENDIX

Supreme Court, U.S.
FILED
DEC 16 2010
OFFICE OF THE CLERK

No. 09-1159

IN THE

Supreme Court of the United States

BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY,

Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

JOINT APPENDIX

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PETITION FOR CERTIORARI FILED MARCH 22, 2010
CERTIORARI GRANTED NOVEMBER 1, 2010

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The following opinions, decisions, judgments and orders have been omitted in printing this joint appendix because they appear on the following pages in the appendix to the Petition for Certiorari:

Opinion of the United States Court of Appeals for the Federal Circuit ..... Pet. App. 1a

Opinion of the United States District Court for the Northern District of California ..... Pet. App. 29a

Order of the United States Court of Appeals for the Federal Circuit denying petition for rehearing and rehearing *en banc* ..... Pet. App. 75a

Case Details

U.S. Court of Appeals for the Federal Circuit

BD TRUSTEE LELAND V ROCHE MOLECULAR

2008-1509

Date	History
---	.
10/14/2008	Appellant Principal Brief Filing Date
11/25/2008	Appellee or Cross Appellant Principal Brief Filing Date
1/21/2009	Appellant Reply Brief Filing Date
2/20/2009	Cross Appellant Reply Brief Filing Date
3/2/2009	Appendix Filing Date
5/5/2009	Oral Argument Date / Calendared
9/30/2009	Disposition: Affirmed-in-Part, Vacated-in-Part, and Remanded ; by Panel
12/29/2009	Mandated on
>>	*Please Note: The briefs above are only the most current.*<<

MOTIONS AND OTHER ENTRIES

>>Please Note: Motions are listed first. Entries are listed last.<<

11/13/2009	**MOTION**: Entry 52 :by Other — Motion for leave to file a brief as amici curiae in support of

Stanford's petition for rehearing or rehearing en banc. (Amici curiae brief submitted with motion)
SERVICE : by Mail on 11/13/2009

REPLY 1: 11/19/2009 , Entry # 57

ACTION: Entry 53: Granted.
Filed: 11/18/2009

* * *

>> Entries for Case Number: 2008-1509 <<

Entry 63 :	11/1/2010 : Notice from the Clerk of the Supreme Court of the United States indicating that the Court has granted the petition for a writ of certiorari.
Entry 61 :	3/25/2010 : Notice from the Clerk of the Supreme Court of the United States indicating that a petition for writ of certiorari was filed on 3/22/2010 and placed on the docket as No. 09-1159, Bd. of Trustees of Leland Stanford Junior University v. Roche Molecular.

* * *

Entry 49 :	5/5/2009 : Submitted after ORAL ARGUMENT by Ricardo Rodriguez and Adrian M. Pruetz. Panel: Linn, Prost and Moore.
Entry 48 :	4/24/2009 : Cross Appellants Roche Molecular Systems, Inc.'s response to Appellant's Board of Trustees of the Leland Stanford

Junior University's supplemental authority. (Sent to Panel)

SERVICE : by Mail on 4/23/2009

Entry 47 : 4/22/2009 : Appellant Stanford Junior University's response to Roche's April 14, 2009 notice of supplemental authority and their supplemental authority. (sent to panel)

SERVICE : by Mail on 4/21/2009

Entry 46 : 4/15/2009 : Roche Diagnostics Corporation's, et al. supplemental authority. (Sent to Panel0

SERVICE : by Mail on 4/14/2009

* * *

Entry 26 : 9/4/2008 : Docketing Statement for appellant, The Board of Trustees of the Leland Stanford Junior Universi.ty.

SERVICE : by Mail on 9/3/2008

* * *

Entry 19 : 8/26/2008 : Docketing Statement for cross-appellants, Roche Molecular Systems, Inc., et al.

SERVICE : by Mail on 8/25/2008

* * *

Entry 3 : 8/12/2008 : Official Caption.

SERVICE : by Court on 8/12/2008

DOC : Bd Trustee Leland 2008-1509 (8.12.08 CAPTION).pdf

Entry 2 :	8/12/2008 : NOTE TO THE FILE: Appeal 2008-1509 and Cross Appeal 2008-1510 (both docketed on 8/12/08) are consolidated.

* * *

Briefs

* * *

2/27/2009	Corrected Appendix (Volumes III and IV) . BY The Board of Trustees of the Leland Stanford Junior University (Appellant). SERVED BY Mail ON 3/13/2009. FILED ON 2/27/2009. (CONFIDENTIAL & NON-CONFIDENTIAL VERSIONS)
2/20/2009	Reply Brief of Defendants/Counterclaimants-Cross Appellants Roche Molecular Systems, Inc., Roche Diagnostics Corporation and Roche Diagnostics Operations, Inc. BY Roche Diagnostics Corporation, et al. (Cross-Appellants). SERVED BY Mail ON 2/20/2009. FILED ON 2/20/2009. (NON-CONFIDENTIAL)
1/21/2009	Response and Reply Brief of the Board of Trustees of the Leland Stanford Junior University, Plaintiff/Counterclaim Defendant-Appellant . BY The Board of Trustees of the Leland Stanford Junior University (Appellant).

	SERVED BY Mail ON 1/21/2009. FILED ON 1/21/2009. (NON-CONFIDENTIAL
11/25/2008	Principal Brief of Defendants/CounterClaimants-Cross Appellants Roche Molecular Systems, Inc., Roche Diagnostics Corporation and Roche Diagnostics Operations, Inc. . BY Roche Molecular Systems, Inc., et al. (Cross-Appellants). SERVED BY Mail ON 11/25/2008. FILED ON 11/25/2008. (NON-CONFIDENTIAL)
10/14/2008	Principal Brief of the Board of Trustees of the Leland Stanford Junior University, Plaintiff/Counterclaim Defendant-Appellant . BY The Board of Trustees of the Leland Stanford Junior University (Appellant). SERVED BY Mail ON 10/14/2008. FILED ON 10/14/2008 . (NON-CONFIDENTIAL)
	Rehearings
10/30/2009	Entry 51 : Appellant [The Board of Trustees of the Leland Stanford Junior University]-Combined Petition for Panel Rehearing and Rehearing En Banc. Mail Service-10/30/2009. Filed: 10/30/2009.
	Response requested from: Cross-Appellants (Roche Molecular Systems, Inc.). Response due:

11/30/2009. Response filed:
11/25/2009

Entry 60: Petition/En Banc Action:
Denied/Denied on 12/22/2009.

U.S. District Court
California Northern District (San Francisco)
CIVIL DOCKET FOR CASE #: 3:05-cv-04158-MHP

Board of Trustees of the Leland Stanford Junior University v. Roche Molecular Systems, Inc. et al
Assigned to: Hon. Marilyn H. Patel
Case in other court: 08-01509; 08-01510
Cause: 35:271 Patent Infringement

Date Filed: 10/14/2005
Date Terminated: 01/08/2010
Jury Demand: Both
Nature of Suit: 830 Patent
Jurisdiction: Federal Question

Date Filed	#	Docket Text
10/14/2005	1	COMPLAINT; Demand for Jury Trial against Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc., Roche Diagnostic Systems, Inc. (Filing fee $ 250.00, receipt number 5513257.). Filed byBoard of Trustees of the Leland Stanford Junior University. (gba, COURT STAFF) (Filed on 10/14/2005) Additional attachment(s) added on 10/24/2005 (gba, COURT STAFF). (Entered: 10/17/2005)
		* * *

11/17/2005	15	*Defendants'* ANSWER to Complaint with Jury Demand, COUNTERCLAIM against Thomas Merigan, Board of Trustees of the Leland Stanford Junior University byRoche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc.. (Stone, Robert) (Filed on 11/17/2005) (Entered: 11/17/2005)
11/17/2005	16	STIPULATION *of Dismissal of Complaint as to Roche Diagnostic Systems, Inc.* by Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc., Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc.. (Stone, Robert) (Filed on 11/17/2005) (Entered: 11/17/2005)
	* * *	
12/21/2005	20	*Stanford's Reply to Counterclaims and Merigan's* ANSWER to Counterclaim byBoard of Trustees of the Leland Stanford Junior University, Thomas Merigan, Board of Trustees of the Leland Stanford Junior University. (Rodriguez, Ricardo) (Filed on

		12/21/2005) (Entered: 12/21/2005)
		* * *
08/04/2006	65	ANSWER TO COUNTERCLAIM *(AMENDED) by Thomas Merigan, Mark Holodniy and* byBoard of Trustees of the Leland Stanford Junior University. (Rodriguez, Ricardo) (Filed on 8/4/2006) (Entered: 08/04/2006)
		* * *
10/20/2006	76	NOTICE by Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc. *STATEMENT OF ISSUES FOR SUMMARY JUDGMENT* (Stone, Robert) (Filed on 10/20/2006) (Entered: 10/20/2006)
10/20/2006	77	NOTICE by Board of Trustees of the Leland Stanford Junior University *Statement of Issues for Summary Judgment* (Rhyu, Michelle) (Filed on 10/20/2006) (Entered: 10/20/2006)
		* * *
10/27/2006	90	MOTION for Summary Judgment *Of Ownership Of And License to The '730 And '705 Patents (REDACTED VERSION) filed by Roche Molecular Systems, Inc., Roche Diagnostics*

		Corporation, Roche Diagnostics Operations, Inc.. Motion Hearing set for 12/4/2006 02:00 PM in Courtroom 15, 18th Floor, San Francisco. (Stone, Robert) (Filed on 10/27/2006) Modified on 11/6/2006 (gba, COURT STAFF). (Entered: 10/27/2006)
10/27/2006	[80-87, 89]	[Declarations, Proposed Orders, and Motion to Seal relating to 90-Roche Motion for Summary Judgment]
	* * *	
10/27/2006	92	MOTION for Summary Judgment *Counterclaim Defendants Stanford University, Dr. Merigan and Dr. Holodniy's Notice of Motion and Motion for Summary Judgment* filed by Board of Trustees of the Leland Stanford Junior University. Motion Hearing set for 12/4/2006 02:00 PM in Courtroom 15, 18th Floor, San Francisco. (Rhyu, Michelle) (Filed on 10/27/2006) (Entered: 10/27/2006)
	* * *	
10/27/2006	96	Brief re 92 MOTION for Summary Judgment *Counterclaim Defendants Stanford University, Dr. Merigan and Dr. Holodniy's Notice of Motion and Motion for*

		Summary Judgment Counterclaim Defendants Stanford University, Dr. Merigan and Dr. Holodniy's Motion for Summary Judgment filed byBoard of Trustees of the Leland Stanford Junior University. (Attachments: # 1 Public Brief PART 2 of 2)(Related document(s) 92) (Rhyu, Michelle) (Filed on 10/27/2006) (Entered: 10/27/2006)
		* * *
10/27/2006	99	MOTION for Summary Judgment of Ownership of and License to the '730 and '705 Patents; and Memorandum of Points and Authorities in Support REDACTED VERSION filed by Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc.. Motion Hearing set for 12/4/2006 02:00 PM in Courtroom 15, 18th Floor, San Francisco. (gba, COURT STAFF) (Filed on 10/27/2006) (Entered: 11/14/2006)
10/27/2006	[100 - 106]	[Declarations relating to 99 Roche Motion for Summary Judgment]
		* * *

10/27/2006	170	MOTION for Summary Judgment filed by Board of Trustees of the Leland Stanford Junior University, Dr. Merigan and Dr. Holodniy's. FILED UNDER SEAL (gba, COURT STAFF) (Filed on 10/27/2006) (Entered: 07/02/2007)
10/27/2006	[164 - 169, 171]	[Declarations relating to 170-Stanford Motion for Summary Judgment]
	* * *	
11/15/2006	107	STIPULATION *JOINT STATEMENT OF UNDISPUTED FACTS* by Board of Trustees of the Leland Stanford Junior University, Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc., Thomas Merigan, Board of Trustees of the Leland Stanford Junior University, Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc.. (Stone, Robert) (Filed on 11/15/2006) (Entered: 11/15/2006)
	* * *	
11/15/2006	111	Memorandum in Opposition re 90 MOTION for Summary

		Judgment *Of Ownership Of And License to The '730 And '705 Patents Stanford University, Dr. Merigan and Dr. Holodniy's Opposition to Counterclaimant RMS's Motion for Summary Judgment* filed byBoard of Trustees of the Leland Stanford Junior University. (Rhyu, Michelle) (Filed on 11/15/2006) (Entered: 11/15/2006)
11/15/2006	[112 - 117]	[Declarations, affidavit, and proposed order relating to 111- Stanford Opposition to Roche Motion for Summary Judgment]
		* * *
11/15/2006	118	Memorandum in Opposition re 92 MOTION for Summary Judgment *Counterclaim Defendants Stanford University, Dr. Merigan and Dr. Holodniy's Notice of Motion and Motion for Summary Judgment* filed byRoche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc.. (Boozell, Jeffrey) (Filed on 11/15/2006) (Entered: 11/15/2006)
11/15/2006	[108 - 110]	[Declarations relating to 118- Roche Opposition to Stanford Motion for Summary Judgment]
		* * *

12/06/2006	132	OBJECTIONS to *Evidence Offered in Support of Counterclaim Defendants' Motion for Summary Judgment and Opposition to Roche's Motion for Summary Judgment* by Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc.. (Chiang, Tun-Jen) (Filed on 12/6/2006) (Entered: 12/06/2006)
12/08/2006	133	Minute Entry: Motion Hearing held on 12/7/2006 before Judge Marilyn Hall Patel re 92 MOTION for Summary Judgment, 90 MOTION for Summary Judgment, 120 MOTION to Strike. Matters deemed submitted. Stanford's Documents for in camera review: The court rules that Exhibits 1-5, and 7, shall be disclosed. The claim of privilege is denied. Exhibit 6 documents are privileged; they shall not be disclosed. Roche's Documents: The single Exhibit 1 is not privileged, and therefore must be disclosed. Defendant's Objections [#132] filed 12/6/06 are stricken as untimely. (Court Reporter Connie Kuhl.) (epb, COURT STAFF) (Date Filed: 12/8/2006)

		(Entered: 12/08/2006)
12/15/2006	134	TRANSCRIPT of Proceedings held on 12/7/06 before Judge Marilyn H. Patel. Court Reporter: Connie Kuhl. (hdj, COURT STAFF) (Filed on 12/15/2006) (Entered: 12/20/2006)
		* * *
02/23/2007	139	ORDER by Judge Marilyn Hall Patel denying 90 Defendants' Motion for Summary Judgment, granting in part and denying in part 92 Plaintiff's Motion for Summary Judgment. (epb, COURT STAFF) (Filed on 2/23/2007) (Entered: 02/23/2007)
		* * *
03/12/2007	144	MOTION Certification of Memorandum and Order re Cross Motions for Summary Judgment and Request for Stay of Proceedings filed by Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc.. Motion Hearing set for 3/19/2007 03:00 PM in Courtroom 15, 18th Floor, San Francisco. (Attachments: # 1 Proposed Order)(Chiang, Tun-Jen) (Filed on 3/12/2007) (Entered: 03/12/2007)

	* * *	
03/23/2007	148	Memorandum in Opposition re 144 MOTION Certification of Memorandum and Order re Cross Motions for Summary Judgment and Request for Stay of Proceedings filed byBoard of Trustees of the Leland Stanford Junior University. (Attachments: # 1 Proposed Order)(Rodriguez, Ricardo) (Filed on 3/23/2007) (Entered: 03/23/2007)
03/26/2007	149	AMENDED COMPLAINT *(First)* against Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc.. Filed byBoard of Trustees of the Leland Stanford Junior University, Mark Holodniy, Thomas Merigan, Board of Trustees of the Leland Stanford Junior University. (Attachments: # 1 Exhibit A# 2 Exhibit B# 3 Exhibit C)(Rodriguez, Ricardo) (Filed on 3/26/2007) (Entered: 03/26/2007)
	* * *	
03/30/2007	151	Reply Memorandum *IN SUPPORT OF ITS MOTION FOR CERTIFICATION* filed byRoche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics

		Operations, Inc.. (Attachments: # 1 Exhibit 1)(Cannon, Brian) (Filed on 3/30/2007) (Entered: 03/30/2007)
04/02/2007	152	TRANSCRIPT of Proceedings held on 3/19/07 before Judge Marilyn H. Patel. Court Reporter: Sahar McVickar. (gba, COURT STAFF) (Filed on 4/2/2007) (Entered: 04/03/2007)
		* * *
04/09/2007	154	Minute Entry: Motion Hearing held on 4/9/2007 before Judge Marilyn Hall Patel (Date Filed: 4/9/2007) re 144 MOTION Certification of Memorandum and Order re Cross Motions for Summary Judgment and Request for Stay of Proceedings (Court Reporter Juanita Gonzales.) (awb, COURT-STAFF) (Date Filed: 4/9/2007) (Entered: 04/09/2007)
04/13/2007	155	*DEFENDANTS'* ANSWER to Amended Complaint, Amended COUNTERCLAIM against Board of Trustees of the Leland Stanford Junior University, Mark Holodniy, Thomas Merigan byRoche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc.. (Cannon, Brian) (Filed on 4/13/2007)

		(Entered: 04/13/2007)
04/16/2007	156	MEMORANDUM AND ORDER by Judge Marilyn Hall Patel denying 144 defendant's motion for certification and request to stay proceedings (awb, COURT-STAFF) (Filed on 4/16/2007) (Entered: 04/16/2007)
04/16/2007	157	MEMORANDUM AND ORDER DENYING defendant Roche's motion for summary judgment AND GRANTING IN PART/DENYING IN PART plaintiff's motion for summary judgment; Signed by Judge Marilyn Hall Patel on 4/16/2007; (awb, COURT-STAFF) (Filed on 4/16/2007) (Entered: 04/16/2007)
04/23/2007	158	TRANSCRIPT of Proceedings held on 4/9/07 before Judge Marilyn H. Patel. Court Reporter: Juanita Gonzalez. (gba, COURT STAFF) (Filed on 4/23/2007) (Entered: 04/24/2007)
04/30/2007	159	ANSWER TO FIRST AMENDED COUNTERCLAIM by Mark Holodniy, Thomas Merigan, Board of Trustees of the Leland Stanford Junior University. (Rhyu, Michelle) (Filed on 4/30/2007) Modified on 5/3/2007 (gba, COURT STAFF). (Entered: 04/30/2007)

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05/21/2007		USCA Case Number Misc. No. 854 - In Re Roche Molecular Systems (A Petition for Writ of Mandamus). (gba, COURT STAFF) (Filed on 5/21/2007) (Entered: 05/22/2007)
* * *		
11/27/2007	212	CLAIM CONSTRUCTION MEMORANDUM AND ORDER: Signed by Judge Marilyn Hall Patel on 11/26/2007. (awb, COURT-STAFF) (Filed on 11/27/2007) (Entered: 11/27/2007)
* * *		
02/25/2008	256	MOTION for Leave to File *Motion for Reconsideration of Court's April 16, 2007 Orders Concerning Standing, Ownership and Interlocutory Review* filed by Roche Molecular Systems, Inc.. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Gross, Gabriel) (Filed on 2/25/2008) (Entered: 02/25/2008)
* * *		
02/25/2008	261	MOTION for Summary Judgment *of Invalidity of Patents, CORRECTED to include date, time, place of hearing and presiding judge* filed by Roche Molecular Systems,

		Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc.. Motion Hearing set for 3/31/2008 02:00 PM in Courtroom 15, 18th Floor, San Francisco. (Attachments: # 1 Proposed Order)(Gross, Gabriel) (Filed on 2/25/2008) (Entered: 02/25/2008)
		* * *
02/29/2008	264	Memorandum in Opposition re 256 MOTION for Leave to File *Motion for Reconsideration of Court's April 16, 2007 Orders Concerning Standing, Ownership and Interlocutory Review* filed byBoard of Trustees of the Leland Stanford Junior University. (Attachments: # 1 Exhibit A)(Rhyu, Michelle) (Filed on 2/29/2008) (Entered: 02/29/2008)
		* * *
03/04/2008	272	MEMORANDUM AND ORDER by Judge Marilyn Hall Patel: Stanfords Motion to Amend its Infringement Contentions is GRANTED, Roches Motion to Strike is DENIED, Roches Motion to Amend its Answer is GRANTED, Stanfords Motion to Compel is referred to a Special Master and Roches Administrative Motion to Seal is

		GRANTED.The Clerk is hereby DIRECTED to file Roches Amended Answer and Counterclaims, attached as Exhibit A to their proposed order.(awb, COURT-STAFF) (Filed on 3/4/2008) (Entered: 03/04/2008)
03/05/2008	273	MEMORANDUM AND ORDER by Judge Marilyn Hall Patel: Stanfords motion seeking leave to reconsider is GRANTED only with respect to the construction of PCR and DENIED otherwise, and Roches motion seeking leave to reconsider is DENIED (awb, COURT-STAFF) (Filed on 3/5/2008) (Entered: 03/05/2008)
		* * *
03/24/2008	276	STIPULATION re 258 MOTION for Summary Judgment *of Invalidity of Patents JOINT STATEMENT OF UNDISPUTED FACTS* by Board of Trustees of the Leland Stanford Junior University, Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc.. (Attachments: # 1 Exhibit A)(Chiang, Tun-Jen) (Filed on 3/24/2008) (Entered: 03/24/2008)
03/24/2008	277	Memorandum in Opposition re 258 MOTION for Summary

		Judgment *of Invalidity of Patents* filed byBoard of Trustees of the Leland Stanford Junior University. (Rhyu, Michelle) (Filed on 3/24/2008) (Entered: 03/24/2008)
		* * *
03/31/2008	284	REPLY to Response to Motion re 261 MOTION for Summary Judgment *of Invalidity of Patents, CORRECTED to include date, time, place of hearing and presiding judge* filed byRoche Molecular Systems, Inc., Roche Diagnostics Corporation, Roche Diagnostics Operations, Inc.. (Chiang, Tun-Jen) (Filed on 3/31/2008) (Entered: 03/31/2008)
		* * *
04/11/2008	295	MOTION for Summary Judgment *on Inventorship and Remaining Contract Issues AND NOTICE* filed by Board of Trustees of the Leland Stanford Junior University. Motion Hearing set for 5/26/2008 02:00 PM in Courtroom 15, 18th Floor, San Francisco. (Attachments: # 1 Proposed Order)(Rodriguez, Ricardo) (Filed on 4/11/2008) (Entered: 04/11/2008)
04/11/2008	296	Declaration of Michelle S. Rhyu

		in Support of 295 MOTION for Summary Judgment *on Inventorship and Remaining Contract Issues AND NOTICE* filed byBoard of Trustees of the Leland Stanford Junior University. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Errata 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10, # 11 Exhibit 11, # 12 Exhibit 12, # 13 Exhibit 13, # 14 Exhibit 14, # 15 Exhibit 15)(Related document(s) 295) (Rodriguez, Ricardo) (Filed on 4/11/2008) (Entered: 04/11/2008)
		* * *
05/29/2008	315	MEMORANDUM AND ORDER by Judge Marilyn Hall Patel: Defendant Roches motion for summary judgment of invalidity based on obviousness is GRANTED. Claims 1, 59, 1314, 1819 and 23 of the 730 patent are invalid as obvious. Claims 1, 510 of the 705 patent are invalid as obvious. Claims 14 and 8 of the 041 patent are invalid as obvious. (awb, COURT-STAFF) (Filed on 5/29/2008) (Entered: 05/29/2008)
06/10/2008	316	JUDGMENT; Signed by Judge

		Marilyn Hall Patel on 6/10/2008. (awb, COURT-STAFF) (Filed on 6/10/2008) (Entered: 06/10/2008)
06/13/2008	317	NOTICE OF APPEAL as to 316 Judgment 315 Order on Motion for Summary Judgment by Board of Trustees of the Leland Stanford Junior University, Mark Holodniy, Thomas Merigan. Filing fee $ 455.00. Receipt Number 34611020226.(gba, COURT STAFF) (Filed on 6/13/2008) **(USCA Case No. 2008-1509)** (Entered: 06/23/2008)
		* * *
06/24/2008	327	NOTICE OF CROSS-APPEAL as to 316 Judgment 139 Order on Motion for Summary Judgment 157 Order on Motion for Summary Judgment by Roche Diagnostics Operations, Inc., Roche Molecular Systems, Inc., Roche Diagnostics Corporation. Filing fee $ 455.00. Receipt Number 34611020538. (gba, COURT STAFF) (Filed on 6/24/2008)**(USCA Case No. 2008-1510)** (Entered: 07/08/2008)
		* * *
08/18/2008	332	USCA Case Number 2008-1509 for 317 Notice of Appeal; 2008-1510 for 327 Notice of Cross-

		Appeal. (slh, COURT STAFF) (Filed on 8/18/2008) (Entered: 08/19/2008)
10/15/2009	341	USCA Memorandum affirming-in-part, vacated-in-part, and remanded as to 327 Notice of Appeal, filed by Roche Diagnostics Operations, Inc., Roche Diagnostics Corporation, Roche Molecular Systems, Inc., 317 Notice of Appeal, filed by Mark Holodniy, Thomas Merigan, Board of Trustees of the Leland Stanford Junior University (gba, COURT STAFF) (Filed on 10/15/2009) (Entered: 10/16/2009)
12/31/2009	342	USCA JUDGMENT Affirmed-in-Part, Vacated-in-Part, and Remanded as to 327 Notice of Appeal, filed by Roche Diagnostics Operations, Inc., Roche Diagnostics Corporation, Roche Molecular Systems, Inc., 317 Notice of Appeal, filed by Mark Holodniy, Thomas Merigan, Board of Trustees of the Leland Stanford Junior University (gba, COURT STAFF) (Filed on 12/31/2009) (Entered: 01/05/2010)
01/05/2010	343	CLERKS Letter Spreading Mandate to Counsel (gba, COURT STAFF) (Filed on

		1/5/2010) (Entered: 01/05/2010)
01/08/2010	344	ORDER re DISMISSAL ON REMAND; Signed by Judge Marilyn Hall Patel on 1/6/2010. (awb, COURT STAFF) (Filed on 1/8/2010) (Entered: 01/08/2010)
01/08/2010	345	JUDGMENT; Signed by Judge Marilyn Hall Patel on 1/6/2010. (awb, COURT STAFF) (Filed on 1/8/2010) (Entered: 01/08/2010)

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Plaintiff, vs. ROCHE MOLECULAR SYSTEMS, INC.; ROCHE DIAGNOSTICS CORPORATION; ROCHE DIAGNOSTICS OPERATIONS, INC., Defendants.	CASE NO. C-05-04158 MHP JOINT STATEMENT OF UNDISPUTED FACTS
ROCHE MOLECULAR SYSTEMS, INC. ROCHE DIAGNOSTICS CORPORATION; ROCHE DIAGNOSTICS OPERATIONS, INC., Counterclaimants, vs. THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY; THOMAS MERIGAN AND MARK HOLODNIY Counterclaim-Defendants.	

Pursuant to Civil L.R. 56-2(b) and Judge Patel's standing order, Roche Molecular Systems, Inc., Roche Diagnostics Corp., and Roche Diagnostics Operations, Inc. (collectively "Roche"), the Board of Trustees of the Leland Stanford Junior University ("Stanford"), Thomas Merigan, and Mark Holodniy, respectfully submit this joint statement of undisputed facts.

Roche's Undisputed Facts

Undisputed Fact

1. From 1988 to 1992, Dr. Thomas Merigan was Director of the Center for AIDS Research at Stanford University.

2. Beginning in July 1988, Mark Holodniy was employed by Stanford University as a fellow in the Division of Infectious Diseases.

3. Beginning in October 1988, Mark Holodniy began working in the laboratory of Thomas Merigan.

4. From the period October 1988 to January 1989, Holodniy started on his project by performing PCR experiments at Stanford and reviewing PCR related publications by authors including John Sninsky and Shirley Kwok.

5. By letter dated November 7, 1988, Merigan and David Schwartz of Stanford wrote to Eric Groves of Cetus seeking "a written copy of the Cetus protocol for extraction, amplification and quantitation of HIV DNA. As we are now starting to look at control samples of untreated individuals longitudinally, it is essential that we duplicate the conditions of pcr as run at Cetus."

6. In response to the November 7, 1988 letter, Stanford, Merigan, Schwartz, and Cetus entered into

a material transfer agreement dated December 19, 1988 (the "MTA").

7. Merigan, Schwartz and Stanford executed the MTA in February 1989.

8. Thomas Merigan arranged for Mark Holodniy to visit Cetus.

9. Holodniy was a visitor at Cetus on a regular basis from February 1989 until October or November 1989.

10. Mark Holodniy executed a Visitor Confidentiality Agreement on February 14, 1989.

11. Paragraph 3 of the Visitor's Confidentiality Agreement states:

If, as a consequence of my access to CETUS' facilities or information, I conceive of or make, alone or with others, inventions and improvements thereof or know-how related thereto that relate in any manner to the actual or anticipated business of CETUS, I will assign and hereby do assign to CETUS my right, title, and interest in each of the ideas, inventions and improvements thereof described in this paragraph.

12. Clayton Casipit gave CC2 RNA to Mark Holodniy.

13. By early Fall of 1989, a working assay for the quantitation of HIV RNA copy number had been constructed.

14. While at Cetus, Holodniy received and used horseradish peroxide (HRP) labeled SK-19.

15. While at Cetus, Holodniy received and used gel and reagents for gel electrophoresis.

16. While at Cetus, Holodniy received and used avidin-coated beads and biotin labeled PCR primers.

17. While at Cetus, Holodniy received and used SK-38 and SK-39 primers.

18. Prior to visiting Cetus, Holodniy had never performed HIV RNA extraction.

19. While at Cetus, Holodniy received information relating to HIV RNA extraction.

20. Cetus provided Holodniy with materials to perform HIV RNA extraction.

21. Cetus provided Holodniy with access to equipment to perform HIV RNA extraction while at Cetus.

22. Prior to visiting Cetus, Holodniy had never performed reverse transcription of HIV RNA.

23. While at Cetus, Holodniy received a reverse transcription PCR protocol.

24. Cetus provided Holodniy with materials to perform reverse transcription of HIV RNA.

25. Cetus provided Holodniy with access to equipment to perform reverse transcription of HIV RNA while at Cetus.

26. Prior to visiting Cetus, Holodniy had not amplified HIV RNA using polymerase chain reaction.

27. While at Cetus, Holodniy received advice on how to set up a reverse transcription polymerase chain reaction assay for HIV.

28. Cetus provided Holodniy with access to equipment to conduct amplification of HIV using the polymerase chain reaction while at Cetus.

29. Prior to visiting Cetus, Holodniy had never used a horseradish peroxide (HRP) labeled probe for in detection of PCR product.

30. While at Cetus, Holodniy received advice and suggestions on a procedure to use HRP-labeled probes in the detection of PCR product.

31. In March or April of 1990, an abstract was presented at a UCLA Keystone meeting (the "UCLA Abstract"). The title of the abstract was "Quantitation of HIV-1 RNA in Serum and Correlation with Disease Status Using Polymerase Chain Reaction."

32. The UCLA Abstract names as authors Mark Holodniy, David Katzenstein, Sohini Sengupta, Alice Wang, Clayton Casipit, David Schwartz, Michael Konrad, Eric Groves, and Thomas Merigan.

33. On or about December 20, 1989, Mark Holodniy sent a fax to Eric Groves with a draft of the UCLA abstract.

34. The request included a draft abstract that is the same as the UCLA Abstract later actually presented at the Keystone meeting except that the names Alice Wang, Clayton Casipit and Michael Konrad were added as authors of the final UCLA Abstract.

35. On or about December 27, 1989, Eric Groves sent a letter to Holodniy and Merigan.

36. Eric Grove's letter of December 27, 1989 to Holodniy and Merigan states "Please ask the UCLA Symposia people to keep the information in this abstract confidential until the abstracts are published as the information is subject of a patent application; and, as we discussed, the following people should be included as authors: Alice Wang, M. Konrad."

37. On or about December 22, 1989, Holodniy wrote a letter to Susanne Hennick at UCLA submitting the UCLA abstract.

38. Holodniy's December 22, 1989 letter to Hennick requested that the UCLA abstract be kept confidential prior to the publication of the abstract book.

39. In April 1991, an article was published in the Journal of Infectious Diseases entitled "Detection and Quantification of Human Immunodeficiency Virus RNA in Patient Serum by Use of the Polymerase Chain Reaction" (the "JID Article").

40. The JID Article lists authors as Mark Holodniy, David Katzenstein, Sohini Sengupta, Alice Wang, Clayton Casipit, David Schwartz, Michael Konrad, Eric Groves, and Thomas Merigan.

41. The UCLA Abstract states that: "Quantitation of HIV-1 viral RNA in serum by PCR may be a useful marker for disease progression or monitoring antiviral therapy."

42. The JID Article states that: "Quantitation of infectious HIV RNA in cell-free serum by PCR may be useful as a marker for disease progression or in monitoring anti-viral therapy."

43. The JID Article states that: "Serum PCR may provide an additional marker of disease progression and drag efficacy that could improve our ability to monitor the course of HIV infection. Further studies will be necessary to validate this approach."

44. On or about January 9, 1990, Mark Holodniy submitted an invention disclosure to Cetus.

45. The invention disclosure is entitled "Quantitation of HIV-1 viral RNA in human serum

utilizing an in vitro generated internal standard for coamplification and an enzyme linked affinity assay for detection."

46. The invention disclosure attached a copy of the UCLA Abstract.

47. The article entitled "Reduction in Plasma Human Immunodeficiency Virus Ribonucleic Acid after Dideoxynucleoside Therapy as Determined by the Polymerase Chain Reaction" (the " JCI Article") states that the manuscript for the article was received by the Journal of Clinical Investigation on May 14, 1991.

48. The JCI Article discloses one or more claims of United States Patent No. 5,968,730 (the "'730 patent").

49. The JCI Article discloses one or more claims of United States Patent No. 6,503,705 (the "'705 patent").

50. On May 14, 1992, Thomas Merigan and Michael Kozal filed United States Patent Application No. 07/883,327 (the "'327 application").

51. The '327 application is the parent application of the '730 and '705 patents.

52. The specification of the '730 and '705 patents states, in Section 5.1, that "Serum may be used interchangeably with plasma according to the invention."

53. The '730 patent issued on October 19, 1999 and lists Mark Holodniy, David Katzenstein and Thomas Merigan as named inventors.

54. The '705 patent issued on January 7, 2003 and lists Mark Holodniy, David Katzenstein and Thomas Merigan as named inventors.

55. Paragraph 2 of the MTA states:

The Material that is covered by this Agreement includes: (a) appropriate oligonucleotide primers and probes for the detection of human immunodeficiency virus (HIV), HLA loci and both coded and noncoded control dilutions of HIV in uninfected DNA's to be used as controls for use with CETUS's proprietary polymerase chain reaction (PCR), and associated PCR technology; (b) any related biological material or associated know-how and data that will be received by SCIENTIST from Cetus; and (c) any substance and associated know-how and data that are replicated or derived therefrom by SCIENTIST or his/her co-workers.

56. Paragraph 7 of the MTA states:

SCIENTIST will inform CETUS, in confidence, of research results related to the Material by personal written communication or by providing CETUS with a draft manuscript describing the results of such research. CETUS shall be free to use such data and information for any purpose.

57. Paragraph 8 of the MTA states:

In consideration of CETUS' providing of the Material, INSTITUTION, to the extent it is legally able to do so, hereby grants CETUS the first option to an exclusive license, at a reasonable royalty to be negotiated in good faith based on the respective parties' contributions and relevant industry standards, or at CETUS' option, a nonexclusive license.

58. On July 19, 1991, Cetus and Hoffmann-La Roche, Inc. entered into an Asset Purchase Agreement (the "APA").

59. The Invention Disclosure submitted to Cetus by Michael Konrad on behalf of Mark Holodniy, bearing the identification number 90-003, and entitled "Quantitation of HIV-1 viral RNA in human serum utilizing an in vitro generated internal standard for coamplification and an enzyme linked affinity assay for detection" appears on schedule 2.1(c) of the APA.

60. Holodniy's Visitor's Confidentiality Agreement is listed on Schedule 1.2(d) of the APA, which appears to have been mislabeled and corresponds to Schedule 2.1(d).

61. The MTA is listed on Schedule 1.2(d) of the APA, which appears to have been mislabeled and corresponds to Schedule 2.1(d).

62. Paragraph 12 of the MTA states:

This agreement is not assignable, whether by operation of law or otherwise, without the prior written consent of the Senior Vice President of Research and Development at CETUS.

63. The APA states under "Cetus Corporation" that it is signed by "W. G. Gerber, Senior Vice President"

64. Paragraph 3 of the Material Transfer Agreement states:

As used in this Agreement, "Confidential Information" shall mean all data, protocols, technical and economic information, commercialization, clinical and research strategies, trade secrets and know-how provided by CETUS to SCIENTIST*. SCIENTIST

agrees to take reasonable steps to ensure that all such Material and Confidential Information provided by CETUS (i) will be maintained and held in confidence by SCIENTIST and all SCIENTIST'S personnel involved in research under this Agreement for a period of three (3) years from the termination of the research, (ii) will be used only in connection with research under this Agreement, (iii) will not be made available or transferred by SCIENTIST to any third party without the prior written consent of CETUS, and (iv) will be returned at CETUS' request on termination or expiration of this Agreement. Tile to all such Material and information shall remain in CETUS. SCIENTIST shall take reasonable steps to prevent damage to or loss of any Material. The confidentiality obligations of SCIENTIST hereunder shall not apply to any information which (i) can be shown by SCIENTIST to have been in its possession prior to disclosure to it by CETUS (ii) at the time of disclosure hereunder is, or thereafter becomes, through no fault of SCIENTIST, part of the public domain by publication or otherwise; or (3) is furnished to SCIENTIST by a third party after the time of disclosure hereunder as a matter of right and without restriction on its disclosure.

* and designated in writing as confidential at the time of disclosure.

65. Paragraph 1 of the Visitor's Confidentiality Agreement states:

Acting as consultant and an independent contractor, I will be learning from Dr. Eric Groves and Dr. Michael Konrad of CETUS techniques in molecular biology and Polymerase Chain Reaction assays.

I will be at CETUS from January 15, 1989, through July 1, 1989. During the term of this Agreement, I agree not to perform consulting services in any area involving microbial genetics for any company, corporation, institution, or commercial enterprise (other than affiliates of CETUS).

Stanford's Undisputed Facts

66. The Board of Trustees of the Leland Stanford Junior University ("Stanford") filed suit against Roche Molecular Systems, Inc., Roche Diagnostics Corporation, and Roche Diagnostics Operations, Inc. (collectively, "RMS") on October 14, 2005, for infringement of two U.S. patents: Nos. 5,968,730 (the "'730 patent") and 6,503,705 (the "'705 patent").

67. Roche Molecular Systems filed counterclaims seeking declaratory judgment of its ownership and license to the '730 and '705 patents, as well as to four additional patents and patent applications that are in the same patent family (collectively, "the Merigan Patents"). The additional patents are U.S. Patent Nos. 5,631,128 ("'128 patent", Rhyu Decl., Ex. 555); 5,856,086 ("'086 patent", Rhyu Decl., Ex. 684); 5,650,268 ("'268 patent", Rhyu Decl., Ex. 556), and Reissue Patent No. RE38,352 E ("'352 patent", Rhyu Decl., Ex. 701). The application corresponds to publication US2003/0118986 A1.

68. In the 1980s, Cetus Corporation ("Cetus") was a biotechnology company located in Emeryville, California.

69. In 1983, Kary Mullis, a Cetus employee, invented the polymerase chain reaction, a method for amplifying small amounts of deoxyribose nucleic acid (DNA) into large amounts of DNA. Cetus received numerous patents on this technology.

70. In 1984, Dr. Merigan and Cetus entered into a consulting agreement.

71. In 1988, Drs. Merigan and Schwartz were conducting clinical trials of IL-2 combined with AZT as a therapy for HIV at Stanford. In conjunction with these clinical trials, Drs. Merigan and Schwartz sent blood samples to Cetus. Cetus scientists performed PCR assays of HIV DNA on these samples. These assays looked at levels of proviral DNA in peripheral blood mononuclear cells (PBMCs).

72. Prior to his engagement at Stanford, Dr. Katzenstein was employed at the Food & Drug Administration's Center for Biologics Evaluation Research. As part of his responsibilities at the FDA, Katzenstein had performed PCR experiments.

73. The work that Dr. Holodniy performed between February and November 1989 was published in an abstract at the UCLA Keystone Symposium in March or April 1990. Cetus approved publication of this abstract.

74. The work that Dr. Holodniy performed between February and November 1989 was also published in an abstract and presented at the Sixth International AIDS conference in San Francisco in spring of 1990. Cetus approved publication of this abstract.

75. Cetus consented to publication of both of these abstracts.

76. The JID Article was published with Cetus approval.

77. Additional work that Dr. Holodniy performed with Cetus scientists was published in the Journal of Clinical Microbiology, 29(4):676-79, in April 1991,

under the title "Inhibition of Human Immunodeficiency Virus Gene Amplification by Heparin." Cetus approved publication of this manuscript.

78. A reverse transcription PCR protocol used by Cetus scientists was published in 1989 in Kawasaki E., Amplification of RNA, in: Innis et al., PCR Protocols: a Guide to Methods and Applications, Berkeley, CA: Academic Press, 337-47 (1990). The actual date of publication of this book was December 28, 1989. The JID article cites this as a prior publication at footnote 8. The Kawasaki article indicates that the first reported use of reverse transcription PCR to amplify RNA had been published in 1987 by Veres et al. in The Molecular Basis of the Sparse Fur Mouse Mutation. Science 237:415-17 (1987).

79. The sequences of all four DNA primers used to perform PCR in the JID Article, SK 19, SK 38, SK 39, and SK 145, were published in Kellogg D.B., Kwok S., Detection of Human Immunodeficiency Virus, in: Innis et al., PCR Protocols: a Guide to Methods and Applications, Berkeley, CA: Academic Press, 337-47 (1990). The JID article cites this as a prior publication at footnote 9. Although the citation lists the date of publication as 1990, the actual date of publication was December 28, 1989.

80. The sequence of SK 19 primer was also published in 1987 in Identification of Human Immunodeficiency Virus Sequences by Using In Vitro Enzymatic Amplification and Oligomer Cleavage Detection, J. Virology, 61(5): 1690-94 (1987).

81. The sequences of both the SK 38 and SK 39 primers were also published by Shirley Kwok and

other Cetus scientists in 1988 in Ou et al., DNA Amplifcation for Direct Detection of HIV-1 in DNA of Peripheral Blood Mononuclear Cells, Science, 239:295-297 (1988).

82. The sequence of the SK 145 primer was also published by Cetus in February 1990 in Kwok et al., Effects of Primer-Template Mismatches on the Polymerase Chain Reaction: Human Immunodeficiency Virus Type 1 Model Studies, Nucleic Acids Res., 18(4): 999-1005 (1990).

83. Cetus' protocols for biotinylation of SK 38 and horseradish peroxidase (HRP) labeling of SK 19 were published by Cetus in Levenson C., Chang, C., Nonisotopically Labeled Probes and Primers, in: Innis et al., PCR Protocols: a Guide to Methods and Applications, Berkeley, CA: Academic Press, 1990:337-47 (1990). The JID article cites this as a prior publication at footnote 10. Although the citation lists the date of publication as 1990, the actual date of publication was December 28, 1989.

84. A method of quantitative RT-PCR developed by Alice Wang was published by Cetus in December 1989 in Wang et al., Quantitation of mRNA by the Polymerase Chain Reaction, Proc. Natl. Acad. Sci., 86:9717-21 (1989).

85. A method of quantitative RT-PCR developed by Alice Wang was also disclosed by Cetus in Wang A., Mark D, Quantitative PCR, in: Innis et al., PCR Protocols: a Guide to Methods and Applications, Berkeley, CA: Academic Press, 1990:70-75 (1990). Although the citation lists the date of publication as 1990, the actual date of publication was December 28, 1989.

86. Drs. Merigan, Holodniy, Katzenstein and Dr. Dennis Israelski conducted experiments involving samples from patients who had been treated with dideoxyinosine ("ddI"), both by itself and in combination with the drug AZT.

87. Work of Drs. Merigan, Holodniy, Katzenstein and Israelski using patient samples from ddI trials was published in the article, Holodniy et al., Reduction in Plasma Human Immunodeficiency Virus Ribonucleic Acid after Dideoxynucleoside Therapy as Determined by the Polymerase Chain Reaction, Journal of Clinical Investigation, 88:1755-59 (November 1991) ("JCI Article").

88. The JCI Article states that "plasma HIV RNA copy number can be quantitated and does decrease during dideoxynucleoside therapy."

89. Table 1 and Figures 1, 2, and 3 of the JCI Article correspond to Table 1 and Figures 1, 2, and 3 of each of the patents-in-suit.

90. In May 1991, Dr. Merigan and Cetus Corp. entered into a consulting agreement which had an effective date of April 19, 1991 (the "1991 Merigan Consulting Agreement," Ex. 602).

91. Sometime after May of 1991, Shirley Kwok, an employee at Cetus, wrote a document entitled "Current Status the HIV-2 Assay and a Proposal for Development of an HIV RNA PCR Quantitative Assay." (Kwok Depo. at 85-87) She placed this document in her laboratory notebook between dated July 3, 1991 and August 19, 1991. (Ex. 593 at RMS069922-069931.) The second page of the document states: "I propose that rather than devote the entire lab to HIV-2, that we begin to develop a procedure for quantitation of HIV-1 viral load in

infected patients. Our effort on HIV-2 would be decreased but not terminated. There is a huge demand for quantitative assays to evaluate drug efficacy. A quantitative assay for HIV RNA by PCR would fill this need." (Ex. 593 at RMS 069924.)

92. In 1995, Drs. Holodniy, Merigan, and Katzenstein executed an assignment document purporting to convey their interests in the patents-in-suit to Stanford. Stanford recorded these purported assignments with the PTO on June 9, 1995.

93. The issued patents state that "[t]his invention was made with Government support under contracts AI27762-04 and AI27766-07 awarded by the National Institutes of Health." The patents both state that the Government has certain rights in the patents.

94. Dr. Sninsky read the JCI article around the time it was published. Dr. Sninsky never claimed co-authorship of the JCI article.

95. The FDA declined Cetus' first application for regulatory approval of IL-2 as a therapeutic agent.

96. Section 2.1 of the APA contains an "Agreement to Sell and to Purchase." Schedules 2.1 (a)-(e) and (g) to the APA list specific assets. The 1984 and the 1991 Merigan Consulting Agreements are not listed anywhere in any of these Schedules or in any other part of the APA.

97. The APA also contains a schedule of transferred contracts. This schedule lists Holodniy's 1989 Visitor's Confidentiality Agreement and the 1988 MTA.

98. The APA contains a schedule of intellectual property transferred from Cetus to Hoffmann-La Roche. This schedule lists the invention disclosure

submitted by Michael Konrad on behalf of Mark Holodniy, which has the identification number 90-003. The APA indicates that this invention disclosure rated a "5" on a scale of 1 to 5. Id. The APA indicates "Seller generally seeks patent protection for invention disclosures rated 1,2, or 3." Id. and id. at RMS06456.

99. Certain individuals at RMS knew of the existence of the '730, '086, '128, and '268 patents at least as of December 15, 1999. On or around this date, an RMS patent agent named Doug Petry distributed a memorandum relating to these patents.

100. The Petry memorandum relating to the '730, '086, '128, and '268 patents was distributed to Tom White (Sr. V.P., Research and Development), John Sninsky (V.P., Roche Genetics (U.S.) and V.P., Discovery Research), Stacey Sias (Director of Licensing), Kathy Ordonez (President), Victor Lee (patent counsel), and Melinda Griffith (in-house counsel).

101. At least four of these RMS employees (White, Sninsky, Sias and Griffith) had been Cetus employees.

102. Dr. White was Senior Vice President of Research and Development at Cetus. He was aware that Dr. Merigan had access to Cetus confidential information about PCR and HIV. Dr. White understood that Dr. Merigan's use of PCR to monitor HIV therapy would have been covered by a Cetus consulting agreement.

103. Dr. Tom White, Senior Vice President of Research and Development at RMS, learned of Stanford's efforts to license the '268 and '128 patents to LabCorp in October 1998.

104. The PCR assays that Cetus performed on the patient samples from the IL2/AZT study did not report HIV copy number. The results of the PCR assays that Cetus performed on the patient samples from the IL2/AZT study were expressed as numbers from 1-4, reflecting relatively more or less signal detected in the assay.

105. Paragraph 1 of the Material Transfer Agreement states:

The parties to this Agreement are : Cetus Corporation, hereinafter "CETUS," the Board of Trustees of the Leland Stanford Junior University, hereinafter "INSTITUTION," and Thomas C. Merigan, M.D., and David Schwartz, M.D., Ph.D., hereinafter "SCIENTIST."

106. Paragraph 3 of the Material Transfer Agreement states:

As used in this Agreement, "Confidential Information" shall mean all data, protocols, technical and economic information, commercialization, clinical and research strategies, trade secrets: and know-how provided by CETUS to SCIENTIST *.

* and designated in writing as confidential at the time of disclosure.

107. Paragraph 3 of the Material Transfer Agreement states:

The confidentiality obligations of SCIENTIST hereunder shall not apply to any information which (i) can be shown by SCIENTIST to have been in its possession prior to disclosure to it by CETUS (ii) at the time of disclosure hereunder is, or thereafter becomes, through no fault of SCIENTIST, part of the public domain by publication or otherwise; or (3) is

furnished to SCIENTIST by a third party after the time of disclosure hereunder as a matter of right and without restriction on its disclosure.

108. Paragraph 1 of the Visitor's Confidentiality Agreement states:

I will be at CETUS from January 15, 1989, through July 1, 1989. During the term of this Agreement, I agree not to perform consulting services in any area involving microbial genetics for any company, corporation, institution, or commercial enterprise (other than affiliates of CETUS).

109. Paragraph 2 of the Visitor's Confidentiality Agreement states:

Excluded from the obligations of confidentiality and nonuse agreed to herein is information (i) that I can establish I knew prior to my acquiring it from CETUS; (ii) that I receive from a third party who, when providing it to me; is not under an obligation to CETUS to keep the information confidential; or (iii) that enter the public domain through no fault of mine.

Dated: November 15, 2006

COOLEY GODWARD KRONISH LLP
STEPHEN C. NEAL
RICARDO RODRIGUEZ
MICHELLE S. RHYU

/s/

Michelle S. Rhyu
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Thomas Merigan and Mark
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Dated: November 15, 2006

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HIGHLY CONFIDENTIAL
ATTORNEY'S EYES ONLY

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

THE BOARD OF
TRUSTEES OF THE
LELAND STANFORD
JUNIOR UNIVERSITY,

Plaintiff,

vs. No. C 05-04158-MHP

ROCHE MOLECULAR
SYSTEMS, INC.;
ROCHE DIAGNOSTICS
CORPORATION;
ROCHE DIAGNOSTICS
OPERATIONS, INC.;
ROCHE DIAGNOSTIC
SYSTEMS, INC.,

Defendant.

AND RELATED COUNTERCLAIM

Highly Confidential videotaped deposition of MARK HOLODNIY, M.D., Volume 1, taken on behalf of Defendants and Counterclaimants Roche Molecular Systems, Inc., et al., at 5 Palo Alto Square, Palo Alto, California, beginning at 8:38 a.m. and ending 5:30 p.m. on Wednesday, July 19, 2006, before SUZANNE F. BOSCHETTI, Certified Shorthand Reporter No. 5111.

* * *

Q. Anything else?

A. So the other thing was to also determine and create a standard by which we could actually compare what the amount was in a particular unknown sample.

* * *

Q. Did you also refer to it as the internal cRNA standard?

A. It's possible. It is cRNA because it's derived from a plasmid that we actually can make RNA transcripts from.

* * *

Q. Cetus provided you with that standard; is that correct?

MS. RHYU: Objection. Vague as to "provided."

THE WITNESS: I had had a series of discussions with Cetus scientists about the need for having an internal standard in order to develop a quantitative assay. And we'd had discussions about what might be the best way to put something like this together. I had had these discussions in thinking about it, whether it would be something that would be designed and constructed that would be input into a particular patient sample, or it would be something that would be maintained outside the patient's sample. And there were advantages and disadvantages to that particular strategy.

There was some technical assistance given to me from Cetus personnel in the construction of a standard that actually was put in that assay.

BY MR. STONE:

Q. Cetus provided you with the internal construct that you used in connection with the quantitation assay, correct?

MS. RHYU: Objection. Vague as to "provided you."

THE WITNESS: I had obtained some technical assistance from one of their lab assistants who actually cloned the plasmid and generated the cRNA from that.

BY MR. STONE:

Q. And it was in a tube and he gave it to you, correct?

A. That's correct.

Q. And you used that in connection with the quantitation assay that you were using and that was described in the serum paper, the JID article; is that correct?

A. That's correct.

Q. Had you ever built a quantitation assay prior to your work with Cetus?

A. I had not.

* * *

Q. And you mentioned that you had discussions with certain Cetus scientists about a quantitation assay. Alice Wang was one of those scientists, right?

A. She was one of those scientists.

Q. Who else did you discuss it with?

A. There was another scientist there by the name of Ernie Kawasaki that I had discussions with.

* * *

Q. Did you discuss the quantitation assay with Shirley Kwok or John Sninsky?

MS. RHYU: Objection. Vague as to time.

THE WITNESS: I had – I recall that I had some discussion with Shirley and John about what I was interested in doing. Since they had published some of the early work related to HIV PCR primarily for detection in cells, it was sort of natural for me to talk to Shirley a little about what her work was about when I was at Cetus.

The original work that I was doing at Stanford was all cell based PCR, and it was taking what was known in the literature at the time and making sure that I could actually do that kind of work. And we were successful at Stanford at that time. The thought was in going to Cetus about taking the cell based work and making that quantitative. And so we were really looking at a cell based marker initially and seeing whether that could be made quantitative or not. So Shirley had done some work in that field, as I said primarily for detection, and so I wanted to know what she'd been doing.

* * *

Q. Prior to joining Stanford as an ID fellow, did you have experience with gene expression?

A. I did not.

Q. Prior to joining Stanford as an ID fellow, did you have experience with DNA sequencing?

A. I did not.

Q. Prior to joining Stanford as an ID fellow, had you ever constructed a plasmid?

A. I did not.

Q. Prior to joining Stanford as an ID fellow, did you have experience with DNA extraction?

A. I did not.

Q. Prior to joining Stanford as an ID fellow, did you have any experience with RNA extraction?

A. I did not.

Q. Prior to joining Stanford as an ID fellow, did you have any experience with cloning?

A. I did not.

Q. Prior to joining Stanford as an ID fellow, did you have any experience with running gels?

A. I did not.

Q. Prior to joining Stanford as an ID fellow, did you have any experience working with restriction enzymes?

A. I did not.

Q. Prior to joining Stanford as an ID fellow, had you ever prepared oligonucleotides?

A. I did not.

Q. Prior to joining Stanford as an ID fellow, did you have experience using radioactive isotopes in connection with detection?

A. I did not.

Q. Prior to joining Stanford as an ID fellow, had you ever engaged in any PCR experiments?

A. I did not.

Q. Did you know what PCR was prior to joining Stanford as an ID fellow?

A. I knew only what it meant and what was really in either the public or in the very, very limited

medical literature that was – that was out at that particular time. During my internal medicine residency from 1985 to 1988, there was very, very little that was really published that one could look in the medical – standard medical journals related to that technology. So I was aware of what it was but not the specifics of it.

Q. Did you know that Cetus had invented it?

A. Prior to my arrival or when I –

Q. Prior to your arrival.

A. Not at that time, no.

Q. Did you learn it subsequently to your arrival?

A. Yes.

Q. Did you learn subsequent to your arrival that Kary Mullis of Cetus received the Nobel Prize in connection with that?

A. I don't think that happened prior to my arrival at Stanford.

Q. I'm focusing on subsequent to your arrival.

A. I can't recall the – I know that he actually received the Nobel Prize for the technology. I can't recall the year that that actually was awarded to him.

Q. And when you said for the technology, it was for the PCR technology, correct?

A. That's what my understanding is about the award.

* * *

Q. Have you ever expressly told a third party that you were an expert with respect to PCR technology to your recollection?

A. Not to my recollection.

Q. When you had these discussions with Drs. Merigan and Schwartz about obtaining information from Cetus relating to quantitation of HIV, this is like the January, February 1989 time frame, what did they describe your role to be?

MS. RHYU: I believe that misstates the prior testimony. Objection.

BY MR. STONE:

Q. You can answer the question.

A. My role, to the best of my recollection, was that I would go up to Cetus and have some discussions with Cetus scientists about the feasibility of establishing a quantitative assay.

Q. And the goal then was for you to obtain information from Cetus related to that endeavor?

A. The goal was for us to develop an assay at Stanford that we could use to monitor treatment.

Q. But you didn't develop it at Stanford, you developed it by working at Cetus and obtaining information from them, correct?

MS. RHYU: Objection. Argumentative. Lacks foundation.

THE WITNESS: It was a process over several months, first looking at what we had been doing in the cells at Stanford and then going through several steps in evaluating some of the technical advice that I was getting from some of the Cetus scientists of whether that was going to be a feasible assay or not.

BY MR. STONE:

Q. Ultimately — strike that.

So there was a discussion with Drs. Merigan and Schwartz in the January, February 1989 time frame about you going to Cetus, correct?

A. That's correct.

Q. And ultimately something was arranged that permitted you to go to Cetus, correct?

A. That's correct.

Q. Do you understand what took place that permitted you to go with Cetus?

A. My recollection is that Dr. Merigan had some discussions with people at Cetus. I was not a party to those discussions, but he then came to me to say at that point that he had arranged for me to go up to Cetus and spend some time up there.

* * *

Q. At the time that you – well, strike that.

And your recollection as to the first time you went to Cetus is when?

A. My recollection is that it's the middle of February or somewhere around 1989.

Q. Is there something that leads you to recall that time period as being when you went there?

A. That was when I signed the visitor agreement. And I believe I signed that agreement when I went up there to establish my presence there.

* * *

Q. At the time – so you went to Cetus in or around February 1989 to your recollection, correct?

A. That's correct.

Q. At the time you went there, had you ever constructed a plasmid?

A. I had not.

Q. At the time you went there, had you ever constructed an oligonucleotide?

A. A what?

Q. Oligonucleotide?

A. No, I had not.

Q. At the time you went there, had you ever construct primers necessary for PCR?

MS. RHYU: Objection. Vague as to "constructed."

THE WITNESS: I had not.

BY MR. STONE:

Q. At the time you went there, had you ever worked with restriction enzymes?

A. I had not.

Q. At the time you went there, had you had experience with cloning?

A. I had not.

Q. At the time you went there, had you had experience with HIV RNA extraction from patients' sera?

A. I had not.

Q. At the time you went there, had you run ELISA or PCR product?

A. I had not.

Q.

* * *

Q. At the time you went there, had you amplified HIV RNA?

A. I had not.

Q. At the time you went there, had you quantitated HIV RNA?

A. I had not.

Q. At the time you went there, had you reverse transcribed HIV RNA?

A. I had not.

* * *

Q. And you sought to obtain information from Cetus regarding quantitating both the input and the output of that DNA in the PCR assays; is that correct?

A. That's correct.

Q. Who did you work with to learn that information from Cetus?

MS. RHYU: Objection. Lacks foundation.

BY MR. STONE:

Q. Well, I take it Cetus provided you with information about those topics; is that correct?

A. That's correct.

Q. And who did you work with in obtaining that information from Cetus?

A. So I consulted Drs. Wang and Kawasaki about what might be an approach to actually do that.

* * *

Q. But she had experience, expertise using PCR for quantitation; is that correct?

A. Yes.

Q. And that's why you sought out information from her, correct?

A. Yes.

Q. And you certainly weren't an expert at the time you sought that information from Dr. Wang with respect to quantitating, using PCR for quantitation, correct?

MS. RHYU: Objection. Vague as to "expert."

THE WITNESS: She clearly had been doing experiments and published work in this area that showed the feasibility of doing quantitation. So it seemed like a natural person to approach for this.

BY MR. STONE:

Q. And at that time you approached her, you weren't an expert in that field, correct?

MS. RHYU: Objection. Vague as to "expert."

THE WITNESS: I had not done any previous work in that field.

* * *

Q. You couldn't be an expert if you hadn't done work in the field, right?

A. I hadn't done work in the field.

Q. And you hadn't published in the field?

A. I had not published in the field.

Q. And you were at Cetus to learn information about that field, correct?

A. That's correct.

* * *

Q. Did you obtain any protocols from Cetus for RNA extraction?

A. I don't recall getting a specific written procedure, but I do recall discussions on what kinds of reagents should be used and recipes for those

particular reagents. But not a specifically written-down protocol.

Q. Who did you discuss that with?

A. I discussed that with Dr. Kawasaki.

Q. So he gave you information for performing RNA extraction?

A. Correct.

Q. And was that RNA extraction from sera or was that RNA extraction from cells?

A. Cells.

* * *

Q. Did someone at Cetus give you recipes for RNA extraction that you can recall by name?

A. Yes, it's likely. I also worked with a postdoc that was working with Dr. Kawasaki, and so he also had been doing some of the cellular RNA work. So it's possible that I could have got a protocol from him as well or at least the recipes for the reagents.

* * *

Q. And did Cetus provide you with the reagents to perform RNA extraction?

A. Yes, for the work I was doing up there.

Q. And what reagents did they provide you with? Can you give me a laundry list?

A. There were – there were – the specific nucleic acid extraction reagents, the buffers associated with that. At the time we were using phenol and chloroform extraction, so that material was provided. And the specific primer for the RT, the reverse transcriptase enzyme as well. And the DNA

polymerase and the other primer and the necessary reagents for the PCR reaction.

Q. Did Dr. Kawasaki provide you with information concerning reverse transcription or was that somebody else in the lab at Cetus?

A. He had provided me with some information about reverse transcription, that's correct.

* * *

Q. But the first time that you conducted experiments related to reverse transcription were at Cetus, correct?

A. That's correct.

Q. And the first time that you engaged in RNA extraction was at Cetus, correct?

A. That's correct.

Q. And the first time that you engaged in RNA extraction at Cetus, you did so with instructions and recipes and materials that were provided to you by Cetus, correct?

MS. RHYU: Objection. Vague as to "instructions." Mischaracterizes his prior testimony.

THE WITNESS: I did obtain those particular recipes. Some of the things I did assemble myself by the recipe and did get some of the other necessary reagents to do the extraction in the RT PCR.

BY MR. STONE:

Q. Whatever you assembled yourself, you did so with materials provided to you by Cetus; is that correct?

A. While I was at Cetus, that's correct.

* * *

Q. What materials were you using in September 1989 that you had obtained from Cetus?

A. We were using the probe that was labeled with horseradish peroxidase necessary to generate the color reaction, and we were using the standard that Clayton Casipit had assisted me on in producing.

Q. The standard that Clayton Casipit gave to you in the fall of 1989, correct?

A. Gave to me in the fall of 1989?

Q. Yes.

* * *

Q. So you've mentioned a number of steps in this quantitation assay, and was he providing you information concerning extraction of RNA or was it the RT procedures?

A. I believe it was both.

Q. Okay. And did he provide you with recipes related to RT? And RT is reverse transcriptisves, is that correct – reverse transcription?

A. I can't recall exactly whether he provided me written documentation or it was something that he and I were discussing as he was doing experiments at the time.

* * *

Q. You also mentioned that you received information from Cetus personnel concerning amplification, the PCR steps; is that correct?

A. For amplification?

Q. Yes.

A. Yes.

Q. And who provided you with that information?

A. I think that would have been also Drs. Wang and Kawasaki.

* * *

Q. Cetus also made available to you materials for conducting amplification experiments, correct?

A. That's correct.

Q. And they also made available to you equipment for conducting such experiments, correct?

A. That's correct.

* * *

Q. Whatever equipment you were interested in having access to, they made available to you?

MS. RHYU: Objection. Misstates the testimony.

THE WITNESS: That's correct.

* * *

Q. There was a free flow of information from the Cetus personnel that you interacted with to you concerning PCR, correct?

A. That's correct.

* * *

Q. Dr. Holodniy, when you were at Cetus, did you obtain information from Cetus concerning detection of PCR products?

A. Yes.

* * *

Q. Who did you obtain information from at Cetus concerning methods for isotopic detection of PCR products?

MS. RHYU: Objection. Lacks foundation.

THE WITNESS: I can't recall the specific person.

BY MR. STONE:

Q. You did obtain information but you can't recall from whom you obtained the information?

A. That's correct.

* * *

Q. Cetus provided you with information concerning the creation of the internal cRNA standard that Clayton Casipit gave to you, correct?

MS. RHYU: Objection. Calls for a legal conclusion as to "information." And lacks foundation.

THE WITNESS: The standard was created over a period of time initially with my discussions with Alice, and then how that strategy would go forward with me working with Clayton on how that would be constructed.

BY MR. STONE:

Q. Alice gave you the overall strategy initially; is that what happened?

MS. RHYU: Objection. Mischaracterizes the testimony.

THE WITNESS: I had discussed with Alice the need for a standard and how she had gone about producing a standard previously for the cytokines, and what would be involved in producing a standard that had a gag gene insert. And from there we basically said that we wanted to produce a standard and then how was the best way to sort of execute that.

BY MR. STONE:

Q. And she told you what the best way would be to execute that, correct?

MS. RHYU: Objection. Asked and answered. Mischaracterizes the testimony.

THE WITNESS: She gave me advice and input on an approach that might be usable or feasible to do that.

BY MR. STONE:

Q. Well, you certainly didn't tell her how to build it? You had never built such a standard before, correct?

MS. RHYU: Objection. Argumentative.

THE WITNESS: That's correct.

BY MR. STONE:

Q. So she was telling you how you could go about building, it, correct?

MS. RHYU: Objection. Lacks foundation. Mischaracterizes the testimony.

THE WITNESS: She did give me suggestions and advice about that.

* * *

Q. The internal cRNA standard that was provided to you by Clayton Casipit, how was it constructed?

MS. RHYU: Objection. Assumes facts not in evidence. Vague as "provided to."

BY MR. STONE:

Q. Well, it was constructed?

A. Yes.

Q. And it was given to you by Clayton Casipit. And I'm just wondering what the process was

between when you had the discussion with Alice Wang about this and when it was ultimately handed to you by Clayton Casipit?

A. So the strategy outlined was to look at the gag sequence, which we did, and then determine whether there were any restriction sites where a restriction enzyme could actually cleave that particular DNA sequence of interest in the native form of the HIV gag chain.

And so if one could insert a mutation in that gag chain where a restriction enzyme would no longer be active, then you couldn't cleave the fragment, and therefore the size of that product would be bigger than the native fragment might be.

Q. And this was the strategy that was outlined by Dr. Wang, correct?

MS. RHYU: Objection. Mischaracterizes testimony. Lacks foundation.

THE WITNESS: This was a strategy that Dr. Wang and I had discussed as a possibility.

BY MR. STONE:

Q. Sure, but she outlined it for you? You weren't telling her what the outline of the strategy should be, right?

MS. RHYU: Objection. Asked and answered. Misleading. Mischaracterizes the testimony.

THE WITNESS: In broad terms she did identify this as a strategy. I then went and looked at the HIV specific sequence for what restriction sites were there and whether that was going to be feasible or not.

BY MR. STONE:

Q. So she told you what to do, and then you set off to begin the process of doing it.

MS. RHYU: Objection.

BY MR. STONE:

Q. Is that right?

MS. RHYU: Objection. Mischaracterizes the testimony. Argumentative.

THE WITNESS: So in broad terms, she explained to me what would be necessary in terms of creating those site directed mutants. And it was from there that I had ordered the primers to be able to begin that process to make that particular sequence.

BY MR. STONE:

Q. Did – so she explained the what. Did she also explain the how, how to go about doing that?

MS. RHYU: Objection. Lacks foundation. Mischaracterizes the testimony.

THE WITNESS: She did – she did give me some advice on how I would be able to create a sequence like that.

BY MR. STONE:

Q. And she explained the why also, how this would work –

MS. RHYU: Objection.

BY MR. STONE:

Q. – in connection with the quantitation assay?

MS. RHYU: Objection. Mischaracterizes the testimony. Lacks foundation.

THE WITNESS: She did explain to me how that process would basically show that you could have two different DNA fragments.

* * *

Q. Had you had experience with gene sequencing at that time?

A. I did not.

Q. You testified that at some point in time, you ordered some primers in connection with this effort; is that right?

A. That's correct.

Q. Who assisted you in that regard?

MS. RHYU: Objection. Lacks foundation.

THE WITNESS: In the ordering process of that or –

BY MR. STONE:

Q. Identifying what primers to order.

MS. RHYU: Same objection.

THE WITNESS: I don't specifically recall who – who that might have been.

BY MR. STONE:

Q. Someone assisted you, but you don't recall who it was sitting here today?

A. That's correct.

Q. As you began this effort, were you periodically checking back with Dr. Wang to inform her of your progress?

A. Yes.

Q. To obtain additional guidance from her?

A. To ask her advice, yes.

Q. Certainly not to give her advice, correct?

A. Not about this particular procedure, no.

Q. What was the – what was the next step in connection with the generation of the cRNA standard that you were involved with?

A. The next step was to take that particular sequence and clone that into a plasmid.

Q. At the time that the next step was to clone a generated sequence into the plasmid, had you ever engaged in any cloning experiments?

A. I had not.

Q. And the sequence that you're referring to, what sequence is that?

A. That's an HIV gag gene sequence.

Q. And how is that obtained?

A. It was obtained by several rounds of different PCR reactions in order to make that particular mutated fragment.

Q. And had you ever done that before?

A. No.

Q. And did you receive information from Cetus as to how to do that?

A. Yes.

MS. RHYU: Objection.

BY MR. STONE:

Q. Did that come from Dr. Wang?

MS. RHYU: Wait, wait. Objection to the previous question as to calling for a legal conclusion as to "information."

BY MR. STONE:

Q. Did that information come from Dr. Wang?

A. She provided me with –

MS. RHYU: The same objection. Calling for a legal conclusion as to "information." Just a second. Let me read the question.

Go ahead.

THE WITNESS: She provided me with information on how to construct a mutant gag sequence.

* * *

Q. Previously you had identified a number of nonisotopic detection methods that you had explored for using with PCR products; do you recall that?

A. Yes.

Q. Can you recall which of those nonisotopic detection methods you received information concerning from Cetus?

MS. RHYU: Objection as to information and lacks foundation.

THE WITNESS: The – the assay that – or the – the method that I had received information about was related to a method that would take a PCR product that had biotin incorporated into it and could be somehow captured on some sort of a medium or platform, and then using a hybridization assay with an enzyme-linked probe to detect a color.

BY MR. STONE:

Q. Prior to going to Cetus, had you worked with biotinylated primers?

A. No.

Q. Prior to going to Cetus, had you worked with probes that had been treated with horseradish peroxidase?

A. No.

Q. Prior to going to Cetus, had you worked with avidin beads as a capture method?

A. No.

* * *

BY MR. STONE:

Q. You've identified a number of people that you had interaction with while you were at Cetus. And I want to try to get an exhaustive list. So I'll run through some names and if you can provide me with additional names, I would appreciate it.

A. Okay.

Q. So – and if I mischaracterize people you had interaction with, please let me know.

You've identified Dr. Groves, correct?

A. Correct.

Q. And Dr. Konrad?

A. Correct.

Q. And Dr. Wang?

A. Correct.

Q. And Dr. Kawasaki?

A. Correct.

Q. And Dr. Sninsky?

A. Correct.

Q. And Dr. Gelfand?

A. Correct.

Q. And Clayton Casipit?

A. Correct.

Q. And Sanne DeWitt?

A. Correct.

Q. And I believe you said Sharon DeGroat as well?

A. Correct.

* * *

Q. Is there anyone I've missed?

A. Sue Kim.

Q. Thank you. Is there any – is there anyone else that you interacted with during your months at Cetus?

A. Yes, as I had stated before, Shirley Kwok.

* * *

Q. Did you sign this document on or about February 14, 1989?

A. Yes.

Q. By signing, did you agree to be bound by the terms and conditions of this agreement?

A. Yes.

Q. In the first paragraph it states that you "will be learning from Dr. Eric Groves and Dr. Michael Konrad of CETUS techniques in molecular biology and" – pardon. In the first paragraph it reads that:

> "Acting as a consultant and an independent contractor, I will be learning from Dr. Eric Groves and Dr. Michael Konrad of CETUS techniques in molecular biology and Polymerase Chain Reaction assays."

Do you see that?

A. I do.

Q. And did you learn such techniques from them?

MS. RHYU: Objection. Vague. Compound.

THE WITNESS: I did learn some techniques from Cetus scientists, but not specifically from Drs. Groves and Konrad.

BY MR. STONE:

Q. And those techniques are the techniques and information we were discussing earlier today?

MS. RHYU: Objection. Vague as to "information" and calls for a legal conclusion as to "information."

THE WITNESS: It was the techniques related to the cellular DNA and RNA quantitation and then the serum HIV RNA quantitation.

* * *

Q. The PCR machine that you used at Cetus, is it your recollection that that PCR machine was in the laboratory where you worked?

A. It's my recollection that there was a – that the PCR machine was in that first floor clinical laboratory.

Q. How was it that you'd get access to that equipment, do you recall?

A. As a result of my working in that laboratory, I had access to that piece of equipment.

Q. So if you wanted to use it, you just would go over and use it; is that your recollection?

A. That's my recollection.

* * *

Q. Prior to going to Cetus you had never extracted HIV-1 RNA from sera, correct?

A. That's correct.

Q. And you learned information from Cetus to enable you to do that, correct?

MS. RHYU: Objection. Calls for a legal conclusion as to "information" and as to "enable."

THE WITNESS: I had sought advice from people such as Dr. Kawasaki on the extraction procedures for extracting RNA.

BY MR. STONE:

Q. And he provided you with that information, right?

A. He provided me with –

MS. RHYU: Objection. Objection as to "information." Calls for a legal conclusion.

THE WITNESS: He provided me with the specific elements that would be required for a procedure to extract RNA.

* * *

Q. Cetus provided you with, recipes for extracting HIV-1 RNA from serum, right?

MS. RHYU: Objection. Lacks foundation.

THE WITNESS: They provided me with the specific reagents and the quantities that would be necessary to extract the RNA.

BY MR. STONE:

Q. And then they provided you with the specific materials so you could do that, right?

A. They did provide me with the reagents to do that procedure.

Q. And then they provided you with the equipment so that you could do that, right?

A. That's correct.

Q. The next part of that sentence reads, "reverse transcribed with MLV reverse transcriptase." Do you see that?

A. Yes.

Q. Prior to going to Cetus, you had never reverse transcribed HIV RNA, right?

A. That's correct.

Q. And people at Cetus provided you with information on how to do that, right?

A. That's correct.

MS. RHYU: Objection. Objection as to "information."

BY MR. STONE:

Q. And they provided you with materials so that you could accomplish that, correct?

A. They provided me with reagents to perform reverse transcriptase – reverse transcription.

Q. And they provided you with the equipment so that you could accomplish that as well, correct?

A. That's correct.

Q. The next part of that sentence reads, "and amplified by the polymerase chain reaction using a gag gene primer pair (SK38/39)." Do you see that?

A. Yes.

Q. Prior to going to Cetus, had you amplified HIV RNA?

MS. RHYU: Objection. Asked, and answered.

THE WITNESS: No.

BY MR. STONE:

Q. The individuals that you interacted with at Cetus provided you with information on how to do that, didn't they?

A. To do –

Q. Amplification of HIV RNA?

MS. RHYU: Objection. Misstates the document.

BY MR. STONE:

Q. The product of HIV RNA.

A. They provided me with advice on how to set up a reverse transcription polymerase chain reaction assay for this particular gene.

Q. SK38, do you know what the initials SK refer to?

A. It stands for Shirley Kwok.

* * *

Q. The materials necessary to conduct this amplification was provided to you by Cetus; is that correct?

MS. RHYU: Vague as to time.

THE WITNESS: That's correct.

BY MR. STONE:

Q. And the equipment necessary to do that also provided by Cetus, right?

A. That's correct.

Q. The next part of that sentence references "a biotin labelled upstream primer." Do you see that?

A. Yes.

Q. Prior to working at Cetus, you had never experimented with a biotin labeled upstream primer, correct?

A. That's correct.

Q. Individuals at Cetus with whom you interacted provided you information concerning how to use such an upstream primer, correct?

MS. RHYU: Objection. Calls for a legal conclusion as to "information."

THE WITNESS: They –

MS. RHYU: Vague.

THE WITNESS: They provided me with advice and suggestions to utilizing that particular approach.

BY MR. STONE:

Q. And they also provided you with the biotinylated primer itself, correct?

A. That's correct.

Q. And the equipment with which to use the biotinylated primer in?

A. That's correct.

Q. The next sentence references a "biotinylated PCR product that was liquid hybridized to a horseradish peroxidase conjugated probe." Do you see that?

A. Yes.

Q. Is that the HRP probe that we've discussed previously?

A. That's correct.

Q. And prior to working at Cetus, you had never worked – you had never utilized an HRP probe, correct?

A. That's correct.

Q. And while you worked at Cetus, individuals there provided you with information concerning how to use such a probe, correct?

MS. RHYU: Objection. Calls for a legal conclusion and vague as to "information."

THE WITNESS: They gave me advice and suggestions on a procedure to be able to use that to develop the color reaction.

BY MR. STONE:

Q. And they also provided you with the HRP probe itself, correct?

A. That's correct.

Q. And they provided you with equipment with which to use the probe, correct?

A. That's correct.

Q. The next portion of that sentence reads "bound to avidin." Do you see that?

A. Yes.

Q. Is that a reference to the avidin beads you mentioned previously?

A. Yes.

Q. And prior to working at Cetus, you had never worked with avidin beads, correct?

A. That's correct.

Q. Individuals with whom you interacted at Cetus provided you with information as to how to use such avidin beads?

MS. RHYU: Objection. Calls for a legal conclusion and vague as to "information."

THE WITNESS: They had provided me with advice and suggestions of how that would be incorporated with the biotin PCR product.

BY MR. STONE:

Q. And they also provided you with the avidin beads themselves, correct?

A. That's correct.

Q. And they provided you with the equipment with which to use the avidin beads as part of the colorimetric reaction, correct?

A. That's correct.

Q. In the last paragraph there's reference to "An RNA gag gene sequence being used to quantitate viral copy number." Do you see that second sentence?

A. Yes.

Q. That's the cRNA standard that Clayton provided to you in the fall of 1989?

MS. RHYU: Objection. Vague as to "provided to you."

THE WITNESS: That was the RNA standard that we used in this assay, yes.

BY MR. STONE:

Q. And he handed you a tube that contained that material, correct?

A. That's correct.

Q. And prior to working with Cetus, you had never worked with a standard such as this, correct?

A. That's correct.

* * *

Q. Dr. Holodniy, do you recognize Exhibit 34?

A. Yes.

* * *

Q. And your signature is on the first page of Exhibit 34?

A. Yes, that appears to be my signature.

Q. The brief summary on the first page of Exhibit 34 summarizes the work that's described in the UCLA abstract we were looking at previously?

A. Some of it. The brief summary also details the potential for restriction enzyme digestion of the standard for radioactive or isotopic detection which was not included in the UCLA abstract.

Q. When did you prepare this?

A. I can't recall the date that I would have written this.

Q. On or about January 9, 1990, when you signed it?

A. It's possible.

Q. Do you believe it was done much earlier than that?

A. Probably—not much earlier than that because my recollection of this is it was related to the issue that was brought up earlier from the letter that Dr. Groves had sent Dr. Merigan and myself, which would have been the latter part of December.

Q. The issue about Cetus having proprietary rights in the subject matter of the UCLA abstract and an invention disclosure or patent application existing, right?

MS. RHYU: Objection. Misstates the document.

THE WITNESS: The letter that I wrote to the UCLA symposium indicated that the material was the subject of an invention disclosure, so it would have related to this particular form.

BY MR. STONE:

Q. And this is a Cetus invention disclosure, right?

A. That's correct.

* * *

Q. They provided you with this form because Cetus had an ownership interest with respect to the subject matter of this invention disclosure, right?

MS. RHYU: Objection. Calls for speculation.

THE WITNESS: I believe that's what Dr. Groves was concerned about and interested about when they had instructed me to fill this form out.

BY MR. STONE:

Q. And you didn't reject their request to fill this form out, did you?

A. I did not.

Q. You filled it out and provided it to Cetus, right?

A. That's correct.

* * *

Q. Actually, if we can just go back to Exhibit 34 for just a minute. Sorry about that. On the second page of Exhibit 34 there's a reference to lab notebook, and you said it was your handwriting next to that. Do you see that?

A. Yes.

Q. And it says "personal lab book"?

A. Yes.

Q. Is that a reference to your Stanford lab notebooks?

A. That's correct.

* * *

Q. Could you turn to 16018. What does this page reflect?

A. I believe these are primers that I had ordered related to the development of the construct.

Q. And primers that were generated by Cetus?

A. That's correct.

Q. Okay. Can you turn the page with 16117. Is that something that Paul Gumerlock gave to you?

A. Yes.

* * *

Q. And if you could turn to the page bearing production No. 16165. See at the top it says "cRNA internal standard received purified from Alice Wang Cetus"?

A. Yes.

Q. And this is dated November 6th, 1989?

A. Yes.

Q. And did you receive a purified form of the cRNA internal standard from Dr. Wang on that date?

A. Yes, it appears that I did.

Q. And could you turn to the page – actually, turn to the page with production No. STAN 16144. Do you see the nonisotopic PCR protocol there?

A. Yes.

Q. That' s the same protocol that you gave to Dr. Sengupta?

A. Yes.

Q. And that you received from Cetus?

* * *

THE WITNESS: This was the protocol that I was using at Cetus.

BY MR. STONE:

Q. And if you could turn to the page with production Nos. STAN 16173. Does that page reflect work that you did at Cetus?

* * *

THE WITNESS: Yes, this was an experiment I did conduct at Cetus.

* * *

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiff,

vs.

ROCHE MOLECULAR SYSTEMS, ET AL.,

Defendants

No. C-05-04158-MHP

ROCHE MOLECULAR SYSTEMS, ET AL., LELAND STANFORD JUNIOR UNIVERSITY,

Counterclaimants,

vs.

ROCHE MOLECULAR SYSTEMS, ET AL.,

Counterclaim-Defendants.

ORIGINAL

No. C-04158-MHP

HIGHLY CONFIDENTIAL – ATTORNEY'S EYES ONLY

VIDEOTAPED DEPOSITION OF CLAYTON CASIPIT

Redwood Shores, California

Friday, July 21, 2006

* * *

Q What do you mean by the term "standard"?

A Because it -- well, in the use of quantitative messenger -- quantitating messenger RNA, you need a standard in order to compare against your unknown in order to -- you co-amplify them and then you compare, and then you're able to find out how much RNA is in your unknown.

So the standard is the standard that -- that is -- that needs to be included in your -- in rea- --in the PCR reaction in order to determine the unknown.

Q When you say that the standard has to be included in your PCR reaction, can you be a little bit more specific about that?

A It -- well, it has to be in the same tube and co-amplified. It can also be amplified in a separate tube, but it has to be amplified in the same way. It's more accurate if you put it into the tube, but it -- and based on what the known amount of -- the signal that the known standard gives you, that allows you to extrapolate from that what is your unknown.

Q Have you ever used the CC2 standard for -- in amplification of -- of RNA sequences?

A Yes. It's in the notebooks, yeah, mm-hmm.

Q And did you co-amplify the standard with your sample in the same tube?

A Yes.

Q Is that the only way in which you used the CC2 standard?

A Is that the only way? No. I used it other ways, mainly because once the standard was made, I then needed to characterize it and to ensure that it was

working all right. So I would do it separately in a tube by itself, and then I'd run it under various spiking conditions, which means that I would spike viral lysate into it -- into -- into the tube and then see if I can quantitate the amount of viral lysate that I spiked into it. And then I also ran it on a patient -- or serum samples, patient samples.

Q When you run it with the serum samples, did you have the patient sample and the standard in the same test tube?

A Yes. Those were the last experiments, yeah.

* * *

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

THE BOARD OF
TRUSTEES OF THE
LELAND STANFORD
JUNIOR UNIVERSITY,

Plaintiff,

vs. No. C-05 04158-MHP

ROCHE MOLECULAR
SYSTEMS, INC.;
ROCHE DIAGNOSTICS
CORPORATION;
ROCHE DIAGNOSTICS
OPERATIONS, INC.;
ROCHE DIAGNOSTIC
SYSTEMS, INC.,

Defendant.

AND RELATED COUNTERCLAIM.

Confidential videotaped deposition of DAVID A. KATZENSTEIN, M.D., taken on behalf of Defendants and Counterclaimants Roche Molecular Systems, Inc., et al., at 5 Palo Alto Square, Palo Alto, California, beginning at 9:05 a.m. and ending at 2:30 p.m. on Monday, August 28, 2006, before SUZANNE F. BOSCHETTI, Certified Shorthand Reporter No. 5111.

* * *

Q. Getting back to the idea and the discussion -- I'll call it a discussion or meeting that you had with Dr. Merigan and Dr. Holodniy. At that initial meeting where you -- you discussed the idea, did -- did you discuss or did you propose using this

quantification technique to monitor the effectiveness of therapy?

A. Yes:

Q. And was it your idea at that time in mid-1989 to quantify viral RNA?

A. Yes.

Q. And that's from serum and plasma?

A. Well, whether it was going to be serum or plasma or a particular kind of plasma were the experiments that we needed to carry out, but the idea that you had an analyte that could be measured over time on a regular repeatable basis.

* * *

Q. They were successful, right?

A. They were.

Q. And you published --

MR. RODRIGUEZ: Objection. Vague.

BY MR. CANNON:

Q. And you published the results of those experiments, right?

MR. RODRIGUEZ: The same objection.

THE WITNESS: That's -- well, the -- I believe the JID article is the fulfillment of that idea through a whole series of technical assay development issues that went on over perhaps two years.

* * *

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

THE BOARD OF
TRUSTEES OF THE
LELAND STANFORD
JUNIOR UNIVERSITY,

Plaintiff,

vs. No. C-05 04158-MHP

ROCHE MOLECULAR
SYSTEMS, INC.;
ROCHE DIAGNOSTICS
CORPORATION;
ROCHE DIAGNOSTICS
OPERATIONS, INC.;
ROCHE DIAGNOSTIC
SYSTEMS, INC.,

Defendants.

AND RELATED COUNTERCLAIM

Videotaped deposition of THOMAS C. MERIGAN, M.D., Volume 1, taken on behalf of Defendants and Counterclaimants Roche Molecular Systems, Inc., et al., at 5 Palo Alto Square, Palo Alto, California, beginning at 9:08 a.m. and ending at 1:01 p.m., on Monday, September 11, 2006, before SUZANNE F. BOSCHETTI, Certified Shorthand Reporter No. 5111.

* * *

Q. You directed Dr. Holodniy to go to Cetus?

MR. RODRIGUEZ: Objection. Vague as to "directed."

THE WITNESS: Well, he went there because I arranged it.

* * *

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiff,

vs.

CASE NUMBER: C-05 04158-MHP

ROCHE MOLECULAR SYSTEMS, INC.; ROCHE DIAGNOSTICS CORPORATION; ROCHE DIAGNOSTICS OPERATIONS, INC.

Defendants.

ROCHE MOLECULAR SYSTEMS, INC.; ROCHE DIAGNOSTICS CORPORATION; ROCHE DIAGNOSTICS OPERATIONS, INC.,

Counter-Claimants,

vs.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY; AND THOMAS MERIGAN,

Counterclaim-Defendants

REVISED CERTIFIED COPY

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The video deposition of DAVID H. SCHWARTZ, M.D. was held on Monday, October 16th, 2006, commencing at 9:15 a.m. at the Law Offices of Bowie & Jensen, LLC, 29 West Susquehanna Avenue, Suite 600, Towson, Maryland, 21204, Baltimore, Maryland, before R. Dwayne Harrison, Notary Public.

JOB NO. 54638

* * *

Q Do you recall why Dr. Holodniy was visiting Cetus?

MS. RHYU: Objection. Calls for speculation.

A Yes.

Q And why was that?

MS. RHYU: Same objection.

A At the time that Dr. Holodniy started working on the project, the moleculary agents and the expertise for generating and synthesizing primers was with Cetus. Dr. Kwok had developed several primers and probes that were useful for HIV amplification. I believe Dr. Wang may have been involved in that step but I'm not certain. Dr. Sninsky, as I recall, was involved in the project of quantitation. And at that time thermocycler machines were quite new and I believe Stanford had two but it was my impression that Cetus Corporation had several PerkinElmer. I believe PerkinElmer was the company, thermocyclers.

So it was my understanding that Dr. Holodniy was going to Cetus for access to certain reagents, certain equipment, certain computer programs, I believe, to generate primers and to consult with members of Cetus on scientific issues.

* * *

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Plaintiff, vs. ROCHE MOLECULAR SYSTEMS, INC. ROCHE DIAGNOSTICS CORPORATION; ROCHE DIAGNOSTICS OPERATIONS, INC., Defendants.	CASE No. C–05–04158MHP DECLARATION OF DR. ERIC. S. GROVES IN SUPPORT OF ROCHE'S MOTION FOR SUMMARY JUDGMENT
ROCHE MOLECULAR SYSTEMS, INC.; ROCHE DIAGNOSTICS CORPORATION; ROCHE DIAGNOSTICS OPERATIONS, INC., Counterclaimants, vs. THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY; THOMAS MERIGAN; AND MARK HOLODNIY, Counterclaim-Defendants.	

I, Dr. Eric S. Groves, declare:

1. I have personal knowledge of the facts stated herein. If called upon to testify I could, and would, testify thereto.

* * *

9. Stanford's Drs. Merigan and Schwartz desired to transfer the quantitative PCR capability to their laboratory and so on November 8, 1988, they wrote to me requesting "a written copy of the Cetus protocol for extraction, amplification and quantitation of HIV DNA" using PCR in order to "duplicate the conditions of PCR as run at Cetus." Attached as Exhibit 2 is a copy of the letter I received.

10. As was expected for such requests, as part of maintaining Cetus's intellectual property, in response to Stanford's November 8, 1988 request for Cetus PCR protocols, I understand that Cetus and Stanford entered into additional agreements, including a Materials Transfer Agreement, and permission for a Stanford scientist, Dr. Mark Holodniy to visit Cetus to learn PCR.

11. In February 1989, Dr. Mark Holodniy began visiting Cetus. In order to gain unsupervised access to Cetus equipment, materials and personnel, Dr. Holodniy was required to sign a Visitor's Confidentiality Agreement. Dr. Holodniy was assigned a bench in my laboratory and interacted regularly with members of my laboratory and others at Cetus. Pursuant to agreements between Cetus and Stanford and Dr. Holodniy and Cetus, Dr. Holodniy submitted an invention disclosure in connection with the work he had been doing at Cetus. Attached as Exhibit 3 is a copy of the invention disclosure, which

also attaches an abstract submitted to a UCLA scientific conference.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed this 26th day of October, 2006, at San Diego, California.

/s/

Eric Groves

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Plaintiff, v. ROCHE MOLECULAR SYSTEMS, ET AL., Defendants.	CASE No. C–05 04158–MHP DECLARATION OF THOMAS C. MERIGAN, M.D., IN SUPPORT OF COUNTERCLAIM DEFENDANTS STANFORD UNIVERSITY, DR. MERIGAN AND DR. HOLODNIY'S OPPOSITION TO ROCHE MOLECULAR SYSTEMS' MOTION FOR SUMMARY JUDGMENT
ROCHE MOLECULAR SYSTEMS, ET AL., Counterclaimants, v. THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY; THOMAS MERIGAN; AND MARK HOLODNIY, Counterclaim Defendants.	

I, THOMAS C. MERIGAN, declare:

1. I am the George E. and Lucy Becker Professor of Medicine, Emeritus (active), at Stanford University School of Medicine. I have an M.D. degree from the University of California, San Francisco and

have been employed at Stanford since 1963. I am also a named Counterclaim Defendant in the above-captioned case.

2. I submit this declaration in support of Stanford and Counterdefendants' Opposition to Roche Molecular Systems' Motion for Summary Judgment. I have knowledge of the following, and if called as a witness, I could and would testify thereto.

3. In 1988, I was the Principal Investor at Stanford on a grant from the National Institutes of Health titled Adult AIDS Clinical Trials Unit ("ACTU") that funded a large number of clinical trials. One of the clinical studies conducted at the Stanford ACTU, under the NIH grant, involved AZT and interleukin-2. I hired Dr. David Schwartz to work with me on this study. Dr. Schwartz was an immunologist by training. He held a temporary position in the Stanford ACTU which was renewable on an annual basis. Cetus provided the recombinant interleukin-2 for the study.

4. As part of the study, I suggested that Dr. Schwartz use PCR to attempt to measure the amount of virus in the patient samples. As Cetus had published articles relating to determining the level of HIV in patient samples using PCR, and Cetus was in need of patient samples on which to test its PCR assay, Dr. Schwartz and I agreed to send Cetus patient samples from the IL-2 study for Cetus to conduct a PCR analysis. Some samples were sent to Cetus in the fall of 1988.

5. The results obtained from Cetus showed me that Cetus's PCR test was only semi-quantitative and worked poorly. Around November 7, 1988, Dr. Schwartz and I sent Dr. Eric Groves a letter

requesting the protocol that Cetus had been using, with the idea that we would retry the experiments at Stanford and verify the limitations of the assay. A copy of this letter is attached to the Rhyu Declaration as Exhibit 28.

6. In response to our request for a protocol Cetus sent to Dr. Schwartz and myself a Material Transfer Agreement ("MTA"). A copy of the MTA is attached to the Rhyu Declaration as Exhibit 29.

7. It was my understanding at that time that the MTA applied to the Cetus proprietary PCR protocol that Dr. Schwartz and I intended to repeat using the iterleukin-2 study samples corresponding to the samples we had previously sent to Cetus (the "interleukin-2 PCR experiments"). The proprietary protocol is specifically referred to in paragraph 2 of the MTA. It was my understanding that the MTA applied only to materials given to either myself or Dr. Schwartz in relation to use of the proprietary protocol that Cetus had in December of 1988.

8. It was also my understanding at that time that if the interleukin-2 PCR experiments resulted in an invention, Cetus would have the first option to an exclusive license at a reasonable royalty rate to be negotiated at a later time. If Cetus did not want an exclusive license, it also had the option to take a nonexclusive license to that invention, also at a reasonable royalty rate to be negotiated at a later time. I never understood and never would have understood the MTA to grant Cetus a blanket nonexclusive license with no royalty.

9. I discussed these understandings with Cetus employees, including Jeff Price, at this time.

10. The MTA was not signed until February 1989, in part because it had to be approved by the Stanford Sponsored Projects Office. Soon after the MTA was signed, the interleukin-2 PCR experiments were abandoned because neither Dr. Schwartz nor the Cetus scientists involved had the necessary time or interest to pursue these experiments. Further, it is my recollection that Cetus never sent the requested protocol, and Dr. Schwartz and I never asked for it again. I had concluded by that time that the protocol was too insensitive to give reliable, repeatable results. A better assay was needed.

11. In fact, I don't believe that any materials or information were given to me under this MTA. The MTA states that any "Confidential information" that is transferred under the MTA had to be designated in writing as confidential at the time of the disclosure. I never received any materials or information from Cetus under this agreement that Cetus designated in writing as confidential.

12. During this time period, Dr. Mark Holodniy was also working in my laboratory at Stanford. Dr. Holodniy was interested in developing a better assay for using PCR to detect virus in patient samples.

13. Dr. Holodniy's salary of $26,669 per year was paid under a National Research Service Award AI-07089-09. A copy of the PHS 2271 form and associated signed payback agreement in support of this award are attached to the Supplemental Rhyu Declaration as Exhibit 703.

14. Dr. Holodniy's research in my laboratory was performed under two grants from the National Institutes of Health: AI27762 (the "Center for AIDS Research grant") and AI27666 (the "AIDS Clinical

Trial Group grant"). I note that, in some documents, there is a typographical error that refers to this as the AI27766 grant. Both numbers refer to the same grant.

15. Dr. Holodniy and I decided that he should go to Cetus to work on developing a better quantitative assay. I did not understand or expect that any materials or information that Dr. Holodniy may have access to at Cetus would be covered by the MTA that was signed by me and Dr. Schwartz. I never told Dr. Holodniy about the existence of the MTA, because it never occurred to me that the MTA would apply to Dr. Holodniy. No one from Cetus ever communicated to me that the MTA covered materials that Dr. Holodniy obtained and used at Cetus.

16. Several months after Dr. Holodniy stopped visiting Cetus to work on developing a quantitative assay, he worked with me and Dr. David Katzenstein at Stanford on a different clinical study that followed AIDS patients who had been treated with ddI and AZT. Working with those patients, we developed a method of moitoring the efficacy of HIV treatment using a PCR-based assay, and demonstrated that the assay could be used for determinig the efficacy of treatment.

17. None of the work related to the ddI and AZT study was done in collaboration with Cetus or at Cetus.

18. Our results showing that a reduction in viral RNA load correlated with administration of ddI and AZT treatment was published in the Journal of Clinical Investigation ("JCI") under the title *Reduction in Plasma Human Immunodeficiency Virus Ribonucleic Acid after Dideoxynucleoside*

Therapy as Determined by the Polymerase Chain Reaction.

19. The JCI article demonstrates the usefulness of a PCR based approach for monitoring anti-HIV treatment, which was not appreciated and highly doubted prior to this work.

20. The claims of the '705 and '730 patents capture the discovery demonstrated in the JCI article. Indeed, large portions of the JCI article are reproduced almost verbatim in the patents' specification.

21. In addition to the work of Drs. Holodniy, Katzenstein, and myself, another fellow in my laboratory, Mike Kozal, identified mutations in the HIV reverse transcription gene that could be tracked to follow the efficacy of therapy.

22. The work that Dr. Kozal and I did on detection of HIV gene mutations that could be used to predict the utility of therapy was published under the title HIV-1 Synctium-Inducing Phenotype, Virus Burden, Codon 215 Reverse Transcripitase [sic] Mutation and CD4 Cell Decline in Zidovudine-Treated Patients, J. AIDS, 7:832-38 (1994). This article and the JCI publication formed the basis of the parent application that developed into the '705 and '730 patents. A copy of this article is attached to the Supplemental Declaration of Michelle Rhyu as Exhibit 704.

23. Dr. Kozal's work was done entirely at Stanford. None of it took place at Cetus.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this declaration was

executed in Palo Alto, California on November ___, 2006.

/s/

Thomas C. Merigan, M.D.

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

THE BOARD OF THE TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiff,

vs.

ROCHE MOLECULAR SYSTEMS, INC.; ROCHE DIAGNOSTICS CORPORATION; ROCHE DIAGNOSTICS OPERATIONS, INC.; ROCHE DIAGNOSTIC SYSTEMS, INC.,

Defendants

No. C–05 04158–MHP

CERTIFIED COPY

AND RELATED COUNTERCLAIM

30 (B) (6) VIDEOTAPE DEPOSITION OF LUIS MEJIA

Palo Alto, California
Wednesday, January 9, 2008

Reported by:
KELLI COMBS
CSR No. 7705
Job No. 79005

* * *

Q Is there a funding agreement made between Stanford and the government in connection with the patents involved in the current lawsuit?

A So in that phrase, the second paragraph that you read, I mean, there is two contracts there, and so those -- that would be a funding -- there would be funds that come in from the federal government through those contracts.

Q So do those numbers in that paragraph refer to specific contracts?

A I believe so.

Q Have you ever seen those contracts?

A No, I have not.

Q Have you ever sought to obtain copies of those contracts?

A I believe we have, yes.

Q And were you successful in obtaining copies of those contracts?

MS. RHYU: Objection; vague, misleading.

THE WITNESS: We provided everything to counsel that we found.

BY MR. CANNON:

Q Did you find copies of those contracts?

A I —

MS. RHYU: Again, objection; vague, misleading.

THE WITNESS: I do not believe that we found those particular contracts.

* * *

Revision NOTICE 2 – 1980
November 15, 1980

Stanford University

Administrative Guide

(Guide to Administrative Organization, Policies, and Procedures)

* * *

Inventions, Patents, and Licensing

1. STANFORD POLICY AND PROCEDURE

a. **Invention rights policy** — Unlike industry and many other universities, Stanford's invention rights policy allows all rights to remain with the inventor if possible.

(1) **Retention of patent rights by inventor** — The Board of Trustees on April 14, 1970, adopted the following resolution: "Except in cases where other arrangements are required by contracts and grants for sponsored research or where other arrangements have been specifically agreed upon in writing, it shall be the policy of the University to permit employees of the University, both faculty and staff, and students to retain all rights to inventions made by them."

(2) **Invention rights with external sponsors** — In practice, the great majority of

inventions arise from externally funded research covered by agreements containing patent provisions. Some agreements permit the University to retain title and grant license rights to the sponsor; some provide for the reverse or defer allocation of rights.

(a) **Retention of rights by University** — If the University wishes to obtain title it must petition the sponsor for a waiver and must demonstrate that the best method quickly and effectively to develop a particular discovery is to permit the University to patent and license the invention.

(b) **Retention of rights by inventor** — Some sponsors allow title to be retained by the inventor when the University declines development. In such cases the inventor must petition the sponsoring agency directly. The Sponsored Projects Office's Patent and Copyright Affairs staff can assist in determining the provisions of a particular sponsored research agreement.

* * *

SCHOOL OF MEDICINE
STANFORD UNIVERSITY, STANFORD,
CALIFORNIA 94305 • (415) 723-5715

THOMAS C. MERIGAN, M.D.
GEORGE E. AND LUCY BECKER
PROFESSOR OF MEDICINE AND HEAD,
DIVISION OF INFECTIOUS DISEASES

August 12, 1986

Mark Holodniy, M.D.
Good Samaritan Medical Center
Department of Internal Medicine—LL2
Phoenix, AZ 85006

Dear Dr. Holodniy:

In response to your request, I am enclosing an application for a Division of Infectious Diseases fellowship for 1987, a brief description of our program as it appears in the Stanford University School of Medicine Brochure, and the research interests of the Infectious Diseases faculty. We usually plan a two to three year fellowship period. In addition to filling out this application, we would like to have three letters from individuals who are familiar with your abilities. It would also be useful if you could write a letter yourself describing what you expect to get out of a two year fellowship period in relation to your future goals.

Our fellowships are focused around a specific preceptor-fellow relationship, and the preceptor and fellow are expected to work together to obtain funding for the fellowship period. Such support is currently derived from U.S.P.H.S. research grants and contracts, as well as from private foundation and Stanford University sources. Thus far, we have been successful in obtaining such funds for all fellows accepted to our program. If you have any special support mechanism open to you that may pay your fellowship stipend, such as the armed forces or Public Health Service, it would be important to note this on the application. We feel it is important for a fellow candidate to work with a specific faculty member during his training program in the Division rather than to come to the Division without such a commitment. This, of course, facilitates the investigative undertaking.

In brief, our program represents complete training in infectious disease as it appears in medicine, pediatrics, surgery, surgical subspecialties, and oncology. This is done through the use of consultation both here at Stanford University Hospital and at the Veterans Administration Hospital in Palo Alto and the Santa Clara Valley Medical Center in San Jose. The three hospitals together give a very good cross section of problems in infectious disease, and there are several teaching activities each week for all fellows including all eight faculty members here in Infectious Diseases at Stanford. The fellow who is on the consulting service, approximately 4 months the first year, works with a sub-specialty resident, a faculty member, and one or two medical students in supplying consultations. We also accept certain fellows who do not rotate on the

consulting service, but instead spend a full time commitment in laboratory investigation.

We look forward to receiving your application and letter.

Sincerely yours,

/s/

Thomas C. Merigan, M.D.

tcm:pl

Enclosures

NOTE **See instruction sheet and follow carefully. Complete and submit this form at the time trainee enters training, is reappointed, or the reported appointment is amended. Return Institute/Division copy, green copy, and DRG Statistical copy to the PHS Awarding component. For National Research Service Award (T32) trainees, a signed payback agreement must accompany this form on new and reappointments. PLEASE USE TYPEWRITER.**

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service **STATEMENT OF APPOINTMENT OF TRAINEE**	1. Type 5	Activity T32	I/D Serial No AI070390-09
3. NAME OF TRAINEE (Last, first, initial) HOLODNIY, Mark	2. TYPE OF ACTION ☒ REAPPOINTMENT (Previously supported by this grant)		
5. SOCIAL SECURITY NO. [redacted] / 6. SEX M / 7. Birthdate [redacted]	4. PERMANENT MAILING ADDRESS Division of Infectious Diseases, S156[;] Stanford University, School of Medicine[;] Stanford, CA 94305		
8. U.S. Citizen or U.S. Noncitizen National ☒ Yes OR Permanent Resident of U.S. ☐	9. PRIOR NRSA SUPPORT (individual or institutional) ☐ Yes ☒ No (If YES, See Instructions)		

Yes (See instructions)	

10. EDUCATION – AFTER HIGH SCHOOL (include all academic and professional education. For foreign degrees, give U.S. equivalent.)

NAME OF INSTITUTION, DEPARTMENT & LOCATION	Month and Year Attended		Degree(s) received		MAJOR FIELD	MINOR FIELD
	From	To	Degree	Mo. & Year		
(Most recent) Northwestern University Sch. Med. Chicago, IL	9/81	6/85	M.D.	6/85	Medicine	
Seattle University, Seattle, WA	9/76	6/80	B.S.	6/80	Biology	

11. EMPLOYMENT – AFTER COLLEGE (Include military service, internships and residencies)

NAME AND LOCATION OF EMPLOYER	OCCUPATION OR POSITION TITLE	FROM Mo. & Yr.	To Mo & Yr.
(Most recent) Good Samaritan/ Phoenix VA, Phoenix, Arizona	Resident/ Medicine	7/86	6/88
Good	Intern/	6/85	6/86

Samaritan/ Phoenix VA, Phoenix, Arizona	Medicine		
Swedish Hospital, Seattle, WA	Micro Lab. Tech.	7/80	3/81

12. Names of Specialty Boards	12A. Seeking Certification For N/A	12B. Certified by (include date of certification)
13A. Is Trainee Seeking a Degree? ☐ Yes ☒ No	13B Degree(s) Sought	13C. Month and Year Expected
14A: Discipline, Specialty or Field of Proposed Training Infectious Diseases		14B. Subdiscipline or Subspecialty of Proposed Training Virology

15. Will this Training be taken in an Institution, School, Department other than that entered in item 19?

☐ Yes ☒ No If "Yes," give complete name and address

16. Period of this Appointment From 6/30/88 Thru 6/29/89	17. Approximate percent of trainee's time on this appointment ☒ 100% ☐ 75% ☐ 50% ☐ 25%

18. TRAINING SUPPORT FOR PERIOD OF

APPOINTMENT			
TYPE	This Grant (omit cents)		Other Sources
	TOTAL	MONTHLY	
Stipend	$ 23,004	$ 1,917	
Tuition & fees	(est) 2,865	XXXXXX	
Travel (est.)	800	XXXXXX	
	$ 26,669	XXXXXX	

19. This trainee is qualified for the proposed training and is eligible to receive financial support from this grant for the period specified above. A copy of this appointment form will be given to trainee.

Signature of Program Director	Date
	6/30/88

Typed Name of Program Director

Thomas C. Merigan, M.D.

School	Department		
Medicine	Medicine		

Name and Address of Institution (Street, city, state, zip code)

Stanford University[;] Stanford, CA 94305

20. I certify that the statements herein are true and complete to the best of my knowledge, and that I will comply with all applicable Public Health Service terms and conditions governing my appointment. (A willfully false certification is a criminal offense. U.S.Code,Title 18,Section 1001.)

Signature of Trainee	Date
	6/30/88

TRAINEE COPY

NATIONAL RESEARCH SERVICE AWARD PAYBACK AGREEMENT

This agreement is required under Section 472 of the Public Health Service Act, as amended (42 USC 289l-1), for all individuals who receive a National Research Service Award directly or through an institutional grant other than an award at the prebaccalaureate level.*

I. SERVICE REQUIREMENT — *In accepting a National Research Service Award, I hereby agree to engage in health-related biomedical or health-related behavioral research and/or teaching within two years after termination of my National Research Service Award. This service shall be on a continuous basis, and shall be for a period equal to my total National Research Service Award support in excess of 12 months.*

II. PAYBACK PROVISIONS — *I understand that if I fail to undertake or perform such service in accordance with Section I above, the United States will be entitled to recover from me an amount determined in accordance with the following formula:*

$$A = O\left(\frac{t-s}{t}\right)$$

where "A" is the amount the United States is entitled to recover; "O" is the sum of the total amount paid to me under my National Research Service Award support less the amount paid for the initial 12

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* The National Research Service Award authority, formerly located at section 472 of the Public Health Service Act (42 USC 289l-1) has been recodified in section 487 of the Act (42 USC 288) by the Health Research Extension Act of 1985 (Pub. L. 99-158).

months; "t" is the total number of months in my service obligation; and "s" is the number of months of such obligation served.

Except as provided in Section III below, any amount the United States is entitled to recover shall be paid within the three-year period beginning on the date the United States becomes entitled to recover such amount. Interest on the amount begins on the date the United States becomes entitled to recover such amount and is at the rate fixed by the Secretary of the Treasury after taking into consideration private consumer rates prevailing on that date.

III. CONDITIONS FOR BREAK IN SERVICE, WAIVER AND CANCELLATION – *I hereby understand that the Secretary of Health and Human Services:*

A: May extend the period for undertaking service, permit breaks in service, or extend the period for repayment, if it is determined that:

1. *Such an extension or break in service is necessary to complete my research training;*
2. *Completion would be impossible because of temporary disability; or*
3. *Completion would involve a substantial hardship and failure to extend such period would be against equity and good conscience;*

B: May waive my obligation if it is determined that:

1. *Fulfillment would be impossible because I have been permanently or totally disabled; or*
2. *Fulfillment would involve a substantial hardship and the enforcement of such*

obligation would be against equity and good conscience;

C: Will, in the event of my death, cancel any obligation incurred under this payback agreement.

IV. TERMINATION NOTICE ANNUAL REPORT OF EMPLOYMENT – CHANGE OF ADDRESS AND/OR NAME – *I agree to complete and submit a termination notice immediately upon completion of support. I agree to complete and submit all Annual Payback Activities Certification forms sent to me by the Public Health Service concerning post-award activities, and agree to keep the Public Health Service advised of any change of address and/or name until such time as my total obligation is fulfilled.*

V. PROGRAM EVALUATION – *I understand that I may also be contacted from time to time; but no more frequently than once every two years, after the termination of this award to determine how the training obtained has influenced my career. Any information thus obtained would be used only for statistical purposes and would not identify me individually.*

VI. CERTIFICATION – *In accepting my National Research Service Award, I certify that I will comply with the terms and conditions of this payback agreement.*

Signature /s/ *Date:* June 30, 1988

Support received under PHS Award/Grant No. 5T32 AI-07089-09

Name (Last, First, Middle)

HOLODNIY, Mark

(*Type or Print*)

Mailing Address:

c/o Division of Infectious Diseases,
Room S-156

(*Type or Print*)

Stanford University School of
Medicine

300 Pasteur Drive

Stanford, California 94305

PHS 6031
Rev. 10/85

December 19, 1988

Thomas C. Merigan, M.D.
David Schwartz, M.D., Ph.D.
Division of Infectious Diseases
Stanford University Medical Center
Stanford University
Stanford, CA 94305

RE: MATERIALS TRANSFER AGREEMENT

Dear Drs. Merigan and Schwartz:

Cetus Corporation agrees to provide you with certain research substances and know-how for the purpose of a scientific collaboration under the following conditions:

1. The parties to this Agreement are: Cetus Corporation, hereinafter "CETUS," the "~~Stanford University Medical Center~~," hereinafter "INSTITUTION" and Thomas C. Merigan, M.D., and David Schwartz, M.D., Ph.D., hereinafter "SCIENTIST."
THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY

2. The Material that is covered by this Agreement includes: (a) appropriate oligonucleotide primers and probes for the detention of human immunodeficiency virus (HIV), RLA loci and both coded and noncoded control dilutions of HIV in uninfected DNA's to be used as controls for use with CETUS's proprietary polymerase chain reaction (PCR), and associated PCR technology; (b) any

related biological material or associated know-how and data that will be received by SCIENTIST from CETUS; and (c) any substance and associated know-how and data that are replicated ~~or derived therefrom~~ by SCIENTIST or his/her co-workers. The Material is considered proprietary to CETUS. CETUS shall be free, in its sole discretion, to distribute the Material to others and to use it for its own purposes. It is contemplated that from time to time that SCIENTIST may provide CETUS with certain well characterized samples of individuals at high risk for or with Acquired Immune Deficiency Syndrome (AIDS) or related disorders as established by AIDS Treatment Cooperative Groups, hereinafter (ATCG") and CETUS may use such samples for CETUS' own research purposes.

3. The Material shall be used in research studies on the detection of human immunodeficiency virus (HIV) in samples accumulated by ATCG. During the course of this scientific collaboration, CETUS contemplates providing the SCIENTIST and his/her coworkers with certain proprietary information relating to PCR technology. As used in this Agreement, "Confidential Information" shall mean all data, protocols, technical and economic information, commercialization, clinical and research strategies, trade secrets and know-how disclosed or provided by CETUS to SCIENTIST*. SCIENTIST agrees to take reasonable steps to ensure that all such Material and Confidential Information provided by CETUS (i) will be maintained and held in confidence by SCIENTIST

---

* and designated in writing as confidential at the time of disclosure.

and all SCIENTIST'S personnel involved in research under this Agreement for a period of three (3) years from the termination of the research, (ii) will be used only in connection with research under this Agreement, (iii) will not be made available or transferred by SCIENTIST to any third party without the prior written consent of CETUS, and (iv) will be returned at CETUS' request on termination or expiration of this Agreement. Title to all such Material and information shall remain in CETUS. SCIENTIST shall take reasonable steps to prevent damage to or loss of any Material. The confidentiality obligations of SCIENTIST hereunder shall not apply to any information which (i) can be shown by SCIENTIST to have been in its possession prior to disclosure to it by CETUS (ii) at the time of disclosure hereunder is, or thereafter becomes, through no fault of SCIENTIST, part of the public domain by publication or otherwise: or (iii) is furnished to SCIENTIST by a third party after the time of disclosure hereunder as a matter of right and without restriction on its disclosure.

4. SCIENTIST or INSTITUTION shall not distribute or release the Material in any person other than laboratory personnel under SCIENTIST's direct supervision and shall ensure that no one will be allowed to take or send this Material to any other location, unless written permission is obtained from the Senior Vice President of Research and Development at CETUS. This Material is made available for investigational use only in laboratory animals or in in vitro experiments. SCIENTIST and INSTITUTION agree that the Material will not be used for any other purpose. Neither the Material nor

any biological materials treated herewith will be used in human beings.

5. This Agreement and the resulting transfer of Material constitute a license to use the Material solely for academic or other not-for-profit purposes. Subject to the provisions in paragraph 8, SCIENTIST and INSTITUTION agree that nothing herein shall be deemed to grant to either any rights under any CETUS patents or any rights to use the Material for any products or processes for profit-making or commercial purposes. The Material will not be used in research that is subject to consulting or licensing obligations to another institution, corporation or business entity unless written permission is obtained from the Senior Vice President of Research and Development at CETUS.

6. Subject to the provisions in paragraph 8, SCIENTIST and INSTITUTION shall have no rights in the Material other than as provided in this Agreement, and at the request of CETUS, SCIENTIST will return all unused Material.

7. SCIENTIST will inform CETUS, in confidence, of research results related to the Material by personal written communication or by providing CETUS with a draft manuscript describing the results of such research. CETUS shall be free to use such data and information for any purpose. SCIENTIST agrees to maintain the confidentiality of any information respecting the Material, with the exception, however, that if it is desired to publish or otherwise disclose such information in a noncommercial scientific communication,

SCIENTIST will provide CETUS with a copy of any manuscript or abstract disclosing such information, prior to submission thereof to a publisher or to any third party, and in any case, not less than forty-five (45) days prior to any public disclosure, for the purpose of protecting proprietary or intellectual property of CETUS or INSTITUTION that might be contained in such information. If publication results from research using the Material, SCIENTIST agrees to acknowledge CETUS and/or give credit to CETUS scientists, as scientifically appropriate, based on any direct contribution they may make to the research. CETUS agrees that it will reference or acknowledge SCIENTIST's publications, as scientifically appropriate, in its publications, which may refer to the data developed by SCIENTIST.

8. If the research involving the Material results in an invention or substance that may be commercially useful, SCIENTIST will promptly disclose the invention or substance to INSTITUTION's Patent Administrator and notify the Patent Administrator of CETUS' role as a supplier of the Material used, as well as the role, if any, of any CETUS employee in creating the invention or substance. INSTITUTION, in cooperation with SCIENTIST, will promptly supply CETUS with a copy of the disclosure, in confidence, for CETUS' research and evaluation purposes only. In consideration of CETUS' providing of the Material, INSTITUTION, in the extent it is legally able to do so, hereby grants CETUS the first option to an exclusive license; at a reasonable royalty to be negotiated in good faith based on the respective parties' contributions and relevant industry standards, to use

commercially the invention or substance or at a CETUS' option, a nonexclusive license.

9. The Material is experimental in nature and it is provided WITHOUT WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER WARRANTY, EXPRESS OR IMPLIED. CETUS MAKES NO REPRESENTATION OR WARRANTY THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT OR OTHER PROPRIETARY RIGHT.

10. In no event shall CETUS be liable for any use by SCIENTIST or INSTITUTION of the Material or any loss, claim, damage or liability, of whatsoever kind or nature, which may arise from or in connection with this Agreement or the use, handling or storage of the Material.

11. SCIENTIST and INSTITUTION will use the Material in compliance with all laws and governmental regulations and guidelines applicable to the Material for work with recombinant DNA, and when the Material is used in the United States, SCIENTIST will comply with current NIH guidelines.

12. This Agreement is not assignable, whether by operation of law or otherwise, without the prior written consent of the Senior Vice President of Research and Development at CETUS.

Please return the original of this Agreement to me signed by you and by INSTITUTION's authorized representative; the copy is for your records. The

Material will be shipped as soon as possible upon receipt of this signed Agreement.

Very truly yours,

CETUS CORPORATION

/s/ J. S. Price
Jeffery S. Price, Ph.D.
Senior Vice President
Research and Development

JSP/LSC/TAT:

merigan.mta

/s/ Thomas C. Merigan	2/2/89
Thomas C. Merigan, M.D.	Date
/s/ David Schwartz	2/1/89
David Schwartz, M.D., Ph.D.	Date
/s/ Robert C. Daum	2/24/89
Signature of INSTITUTION's Authorized Representative	Date

ROBERT C. DAUM

Name

CONTRACT OFFICER

Title

Sponsored Projects Office

Address Stanford University
125 Panama
Stanford, CA 94305-4126

EXCERPTS FROM THE LABORATORY
NOTEBOOK OF CLAYTON CASIPIT
SEE SUPP. JA at 1

EXCERPTS FROM THE LABORATORY
NOTEBOOK OF MARK HOLODNIY
SEE SUPP. JA at 3

PUBLICATION CLEARANCE REQUEST
RECEIVED

PATENT DEPARTMENT

IP 89-225

PUBLICATION CLEARANCE REQUEST

NAME OF AUTHOR SUBMITTING REQUEST: Groves, Eric

NAMES OF CO-AUTHORS: M. Konrad, M. Holodniy, D. Katzenstein, Sohini Sengupta, D. Schwartz, Thomas Merigan

WE REQUEST CLEARANCE TO PUBLISH THE ATTACHED MATERIALS ENTITLED: Quantitation of HIV-1 RNA in Serum and Correlation with Disease Status Using the Polymerase Chain Reaction

AS AN ARTICLE IN THE FOLLOWING JOURNAL/BOOK: _____

AS AN ABSTRACT FOR AN ORAL ___ OR POSTER √ PRESENTATION

AT Keystone Meeting 3/31 – 4/7

(GIVE NAME, PLACE AND DATE OF MEETING, SEMINAR, ETC.)

IF ORAL PRESENTATION, THE SPEAKER WILL BE _____

DEADLINE FOR SUBMITTING PUBLICATION
12/20/89

DATE OF REQUEST:_____

IS THE INFORMATION IN THIS PUBLICATION INCLUDED IN A PREVIOUS PUBLICATION CLEARANCE REQUEST? No IS THE INFORMATION IN AN INVENTION DISCLOSURE OR PATENT APPLICATION? Yes IF YES TO EITHER OF THE PREVIOUS QUESTIONS, PLEASE PROVIDE IDENTIFICATION NUMBERS, IF KNOWN_____

PUBLICATION REVIEWER'S ACTION

PROJECT REVIEWER (Please comment on quality and "significance" of research and potential authorship or proprietary issues). Make your best guess as to whether or not this publication may have public relation potential for Cetus.

PR Potential __YES __NO

DEPARTMENT DIRECTOR (Please comment on quality and "significance" of research and potential authorship or proprietary issues). Make your best guess as to whether or not this publication may have public relation potential for Cetus.

PR Potential __YES __NO

CATEGORY I (does not need Patent/Marketing review) CATEGORY II (needs Patent/Marketing review) (Senior R&D management will circle category)

DATE OF CLASSIFICATION _____

SENIOR R&D MANAGEMENT COMMENTS

PATENT COMMENTS (Please indicate if Letter of Confidentiality is advised)

REDACTED **REDACTED**

MARKETING COMMENTS

****

SENIOR R&D MANAGEMENT: DECISION ON PUBLICATION CLEARANCE

_____GRANTED /s/ CONDITIONALLY
_____DENIED

REDACTED

QUANTITATION OF HIV-1 RNA IN SERUM AND CORRELATION WITH DISEASE

STATUS USING THE POLYMERASE CHAIN REACTION.

Alice Wang, Michael Konrad

Mark Holodniy, David A. Katzenstein, Sohini Sengupta, David H. Schwartz, Eric Groves* and Thomas C. Merigan, Division of Infectious Diseases, Stanford University School of Medicine, Stanford, CA. 94305, *Cetus Corporation, Emeryville, CA.

The amount of HIV-1 present in serum may be a potential marker in HIV related disease. A method that detects and quantifies HIV-1 viral RNA in serum is presented. To detect HIV-1 RNA, sera was extracted by a guanadinium thiocyanate method, reverse transcribed with MLV reverse transcriptase and amplified by the polymerase chain reaction using a gag gene primer pair(SK38/39) including a biotin labelled upstream primer. The biotinylated PCR product was liquid hybridized to a horseradish peroxidase conjugated probe, bound to avidin, and quantitated from the optical density of a colorimetric reaction.

Reverse transcription and amplification of known amounts of gag gene RNA and known infectious HIV_{IIIB} virus RNA alone yielded a log-linear relationship between 10 and 10^5 copies of gag RNA and $TCID_{50}$ of virus respectively. No HIV viral RNA was detected in the serum of 3 seronegative healthy controls. In HIV infected patients who were not receiving therapy, serum HIV-1 RNA was detected in 0/5 asymptomatic, 4/5 ARC and 4/5 AIDS patients with copy numbers ranging from 10^2–10^5 of serum. Ultracentrifugation of patient sera revealed detectable signal in pellets, but not supernatant,

indicating that signal is attributable to viral RNA. In addition, extracted material was directly amplified for the presence of viral DNA and gave no detectable signal.

We have demonstrated that HIV-1 viral RNA can be detected and quantitated in patient serum over a four log range. An RNA gag gene sequence was used to quantitate viral copy number. In addition, a nonisotopic enzyme-linked affinity assay in a microtiter plate system allows easy PCR product detection and quantitation. Quantitation of HIV-1 viral RNA in serum by PCR may be a useful marker for disease progression or monitoring antiviral therapy.

RECEIVED
DEC 28 1989
PATENT DEPARTMENT

December 27, 1989

Thomas Merigan, M.D.
Mark Holodniy, M.D.
Stanford University
School of Medicine
Room S-156
Stanford, CA 94305

Dear Drs. Merigan and Holodniy:

This fax is to reiterate in written form the request that I made during Friday's (December 22) discussion. Please ask the UCLA Symposia people to keep the information in this abstract confidential until the abstracts are published as the information is the subject of a patent application; and, as we discussed, the following people should be included as authors: Alica Wang, M. Konrad.

Sincerely,

CETUS CORPORATION

/s/ Eric S. Groves

Eric S. Groves, M.D., Ph.D.
Associate Director
Clinical Research and Development

ESG:cp

cc: K. Kasler
J. Raymond
J. Sninsky

Cetus Corporation, 1400 Fifty-Third Street,
Emeryville, California 94608 Phone: (415) 420-3300
Telex: 4992659 Facsimile: (415) 658-5299

JANUARY 9, 1990 HOLODNIY INVENTION
DISCLOSURE SUBMITTED TO CETUS
SEE SUPP. JA at 14

Detection and Quantification of Human Immunodeficiency Virus RNA in Patient Serum by Use of the Polymerase Chain Reaction[*]

Mark Holodniy, David A. Katzenstein, Sohini Sengupta, Alice M. Wang, Clayton Casipit, David H. Schwartz, Michael Konrad, Eric Groves, and Thomas C. Merigan

Center for AIDS Research, Department of Medicine, Stanford University Medical Center, and Cetus, Emeryville, California; Department of Immunology and Infectious Diseases, Johns Hopkins University Medical Center, Baltimore, Maryland

Human immunodeficiency virus (HIV) RNA was detected and quantified in the serum of HIV-seropostive individuals using the polymerase chain reaction (PCR) and a nonisotopic enzyme-linked affinity assay. Of 55 HIV-infected patients who were not

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[*] Received 23 July 1990; revised 12 October 1990.

Presented in part: VI International Conference on AIDS, San Francisco, 1990 (abstract F.A. 337).

Informed consent was obtained from subjects.

Grant support: National Institutes of Health (AI-27762, -27666, and -07089).

Reprints or correspondence: Dr. Mark Holodniy, Division of Infectious Diseases, Stanford University Medical Center, Stanford, CA 94305.

The Journal of Infectious Diseases 1991;163:862-866

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receiving therapy, serum HIV RNA was detected in 9 of 19 who were asymptomatic, 11 of 16 with AIDS-related complex (ARC), and 18 of 20 with AIDS, with copy numbers ranging from 10^2 to $\geq 5 \times 10^4$/200 μl of serum based on a relationship between absorbance and known copy number of *gag* gene RNA. Linear regression analysis demonstrated a correlation between infectious titer in 42 patient sera cocultured with donor peripheral blood mononoclear cells (PBMC) and PCR product absorbance ($r = .70$, $P < .01$). Serum HIV RNA detected by PCR also correlated with serum p24 antigen positivity, CD4 counts <400/mm^3, and the presence of HIV-related symptoms or disease. Quantification of infectious HIV RNA in cell-free serum by PCR may be useful as a marker for disease progression or in monitoring antiviral therapy.

Quantification of viremia in human immunodeficiency virus (HIV) infection may be an important step in understanding both pathogenesis and treatment in patients with AIDS. Recently, quantitative plasma cultures have been shown to correlate with clinical disease, immunologic impairment, and quantitative assays of p24 core protein in the circulation [1, 2]. Culture techniques may be limited by the requirement for rapid processing, the variability in phytohemagglutinin (PHA)-stimulated donor cells, the long-term maintenance of infectious virus in culture, and the variation in the ability of clinical isolates of HIV to replicate in culture.

With the development of molecular techniques such as gene amplification, it has become possible to detect small numbers of HIV DNA or RNA copies. The polymerase chain reaction (PCR) has been widely applied to the detection of HIV proviral DNA and RNA from peripheral blood mononuclear cells (PBMC) in seropositive patients [3, 4]. In addition, HIV RNA has been detected in plasma [5] by extraction of RNA, reverse transcription, and cDNA PCR.

Here we describe a method to detect and quantitate HIV RNA in patient serum using gene amplification of an HIV-specific gag gene sequence and quantitation of the product with a nonisotopic enzyme-linked affinity assay.

Patients and Methods

Whole blood samples were obtained by venipuncture from 15 seronegative healthy controls and 55 HIV-infected patients. HIV-seropositive patients were clinically assessed according to the Centers for Disease (CDC) criteria [6]. Nine were asymptomatic, 16 had AIDS-related complex (ARC), and 20 met the CDC criteria for AIDS. These corresponded to CDC class II, IVa, and IVc and IVd, respectively. No HIV-infected patient was receiving antiretroviral therapy at the time of specimen collection. Serum was separated within 1 h and stored at −70°C until use.

RNA extraction, reverse transcription, and amplification of cDNA. Total RNA from 200 µl of serum was extracted using guanidinium thiocyanate and reverse transcribed with M-MLV reverse transcriptase by methods previously described [7, 8]. Oligomers used for PCR included SK38, SK39, SK19, and SK145, all of whose sequences have been

published previously [9]. Biotinylation of primer SK38 and horseradish peroxidase (HRP) labeling of probe SK19 were done as described [10]. PCR was carried out in a 100-μl reaction volume as previously described [11] for 30 cycles of amplification in a DNA thermal cycler (Perkin-Elmer Cetus, Norwalk, CT) with the following program: 95°C for 30 s, 55°C for 30 s, 72°C for 60 s, followed by a 10-min extension at 72°C. Negative and positive controls, which included both high- and low-copy-number HIV RNA and DNA, were added at each step. All samples were run in duplicate.

Construction of gag cRNA standard. To construct a standard, SK145 and SK39 were extended and modified to produce linker primers with *Eco*RI and *Kpn*I restriction sites added to each primer respectively. HIV_{IIIB} DNA was amplified with this primer pair to yield a 300-bp *gag* gene product containing the desired restriction sites. Amplified DNA and plasmid pSP72 (Promega, Madison, WI) were digested separately with *Eco*RI and *Kpn*I (New England Bio-labs, Beverly, MA), then ligated under standard conditions in a 1:4 *M* ratio of pSP72 to insert. Transformation of DH5a-competent cells (BRL, Gaithersburg, MD) with the resulting ligated plasmid was carried out according to the supplier's protocol. A clone was obtained that included the 300-bp insert. The insert was then sequenced using the Sequenase 2 kit (United States Biochemical, Cleveland) under standard conditions to verify the correct sequence. Plasmid DNA was transcribed to RNA with a T7 polymerase in vitro transcription kit (Promega). The resulting plasmid and cRNA were quantitated on a spectrophotometer to obtain correct copy number.

Enzyme-linked affinity assay. To detect and quantitate PCR product, 5 μl of PCR product and 45 μl of 5x saline-sodium phosphate-EDTA were heated to 95°C for 5 min and then cooled on ice to denature the sample. Then 1 pmol of SK19-HRP in 5 x Denhardt's solution was added to the denatured PCR product and hybridized for 1 h at 42°C. Next, 100 μl of 2.54-μm polystyrene avidinated beads (Eastman Kodak, Rochester, NY) (~150 pmol of avidin) was added to each well of a 1.2-μm loprodyne membrane-bottom plate (Pall Biosupport, East Hills, NY). The beads were washed with PBS by suspension and filtering on a vacuum filtration holder (Millipore, Bedford, MA). Hybridized PCR product was added to each well containing beads for 20 min. The bead-target-oligomer probe complex was then washed with PBS. A color substrate (*o* phenylenediamine [Sigma, St. Louis]) was added to each well for 10 min. The reaction was stopped with 2 *N* H_2SO_4 and vacuum-filtered into a clear polystyrene microtiter plate (Costar, Cambridge, MA). The absorbance was read at 490 nm on a plate reader (Dynatech, Alexandria, VA).

Serum HIV culture. Fresh PBMC from seronegative blood donors were stimulated in RPMI 1640 medium containing 5 μg/ml PHA and 20% fetal calf serum for 3 days. Patient serum was serially diluted in 24-well culture plates (Costar) and cocultured with 1 x 10^6 washed PHA-stimulated donor cells per well in duplicate as described by Ho et al. [1]. Stocks of HIV_{MN} were produced in acutely infected H-9 cells and their titer determined as the reciprocal of the end-point dilution of virus that resulted in p24 antigen production in H-9 cells after 28 days.

Results

Detection and quantification of HIV RNA was first assessed in reconstruction experiments in which dilutions of HIV_{IIIB} or HIV_{MN} virus stock were added to HIV-seronegative donor serum or *gag* gene cRNA from the plasmid vector was reverse transcribed and amplified in parallel with extracted sera. Reverse transcription and amplification of known amounts of *gag* gene cRNA and infectious HIV_{IIIB} RNA and DNA alone yielded a relationship between absorbance values obtained in the enzyme-linked assay of PCR product and copy number of cRNA and DNA and $TCID_{50}$ of virus (figure 1). The absorbance values obtained were linear between 10^3 and 5×10^4 input copies of *gag* cRNA, 10^2 and 10^4 $TCID_{50}$ of HIV_{IIIB} virus stock, and 10^2 and 10^4 copies of HIV DNA. The use of 5 μl of PCR product in the affinity assay allowed quantification of input DNA and RNA over the widest range of input nucleic acid (10-50,000 copies) and the most linear response (100-10,000 copies; figure 1).

The sensitivity of each step of the assay was determined by the addition of dilutions of infectious virus to serum, cRNA to the reverse transcription reaction, or plasmid DNA to the amplification step. After 30 cycles of amplification,

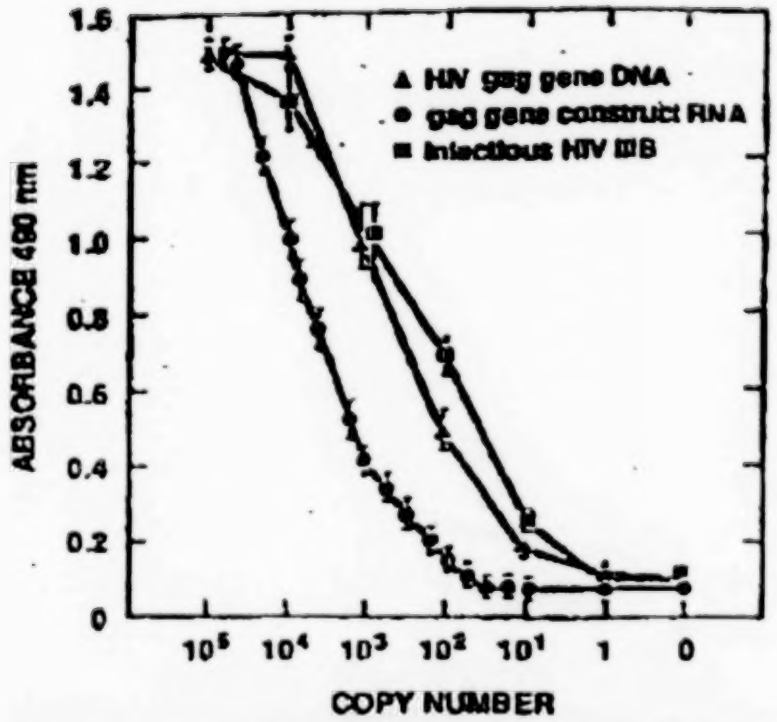

Figure 1. Quantification of infectious human immunodeficiency virus (HIV_{IIIB}) RNA, HIV *gag* gene DNA, and cRNA *gag* gene construct copy number by polymerase chain reaction.

10 $TCID_{50}$ of HIV_{IIIB}, 100 copies of cRNA, and 10 copies of HIV plasmid DNA gave an absorbance that was greater than a negative absorbance cutoff (0.135), defined as the mean absorbance obtained from 15 seronegative sera (0.084 ± 0.017) plus three standard deviations. The use of a greater number of cycles of amplification or >5% of the PCR product increased the sensitivity of the assay for lower copy number but decreased the dynamic range (data not shown).

To test the reproducibility of this assay, 11 sera, 9 from HIV-positive patients and 2 from seronegative controls, were subjected to separate extraction, reverse transcription, and amplification on the same day. Linear regression analysis demonstrated good correlation of mean absorbance values from separate extractions and reverse transcription ($r = .98$, $P < 0.1$

and $r = .94$, $P < .01$, respectively, two-tailed t test) done on the same day. When the same serum samples were extracted on different days, correlation of mean absorbance was somewhat less ($r = .83$, $P < .01$, two-tailed t test). When intraassay variability of the enzyme-linked affinity assay was tested, multiple replicates of the same PCR sample yielded an absorbance that varied <10% between wells.

A series of experiments was carried out to determine the likely origin of signal obtained from extracted sera in this assay. Several lines of evidence point to genomic HIV RNA within virus particles as the source. This was supported by ultracentrifugation, in which signal from sera was found in the pellet fraction, adsorption of signal to immobilized CD4, and deletion of reverse transcriptase to extracted sera, with subsequent amplification resulting in signals below the established cutoff (data not shown).

Sera from 38 of 55 HIV antibody-positive patients demonstrated a positive signal, that is, an absorbance value > 0.135. When the results of PCR were analyzed by the patient's clinical status, 9 of 19 asymptomatic, 11 of 16 ARC, and 18 of 20 AIDS patients had detectable signal. Symptomatic patients, those with ARC and AIDS, were more likely to have detectable signal than asymptomatic patients (29/36 vs. 9/19, $P < .03$, χ^2). The mean absorbance values for each clinical group increased from 0.142 ± 0.05 in asymptomatic patients to 0.267 ± 0.27 and 0.355 ± 0.31 in ARC and AIDS patients, respectively (figure 2). The mean absorbance value for all symptomatic patients (those with ARC and AIDS) was significantly greater than that for asymptomatic

patients (0.316 ± 0.29 vs. 0.142 ± 0.05, $P < .01$, two-tailed t test).

Measurement of viral RNA extracted from serum in this assay was compared with antigen production in cocultures of 10-fold dilutions of serum with PHA-stimulated donor cells. Figure 3 shows the relationship between stage of disease, infectious titer as measured by p24 antigen production in cocultures of serum dilutions, and PCR absorbance in 42 sera. Three sera were culture-positive and negative by PCR (one each asymptomatic, ARC, and AIDS), while 15 were PCR-positive and culture-negative (6 asymptomatic, 5 ARC, and 4 AIDS). Twenty-four sera showed concordance between assays: 7 negative (5 asymptomatic, 1 ARC, and 1 AIDS) and 17 positive (1 asymptomatic, 5 ARC, and 11 AIDS) by both assays. Linear regression analysis of the results obtained from these 42 sera demonstrated a correlation between the titer of infectious virus and PCR product absorbance ($r = .70$, $P < .01$ two-tailed t

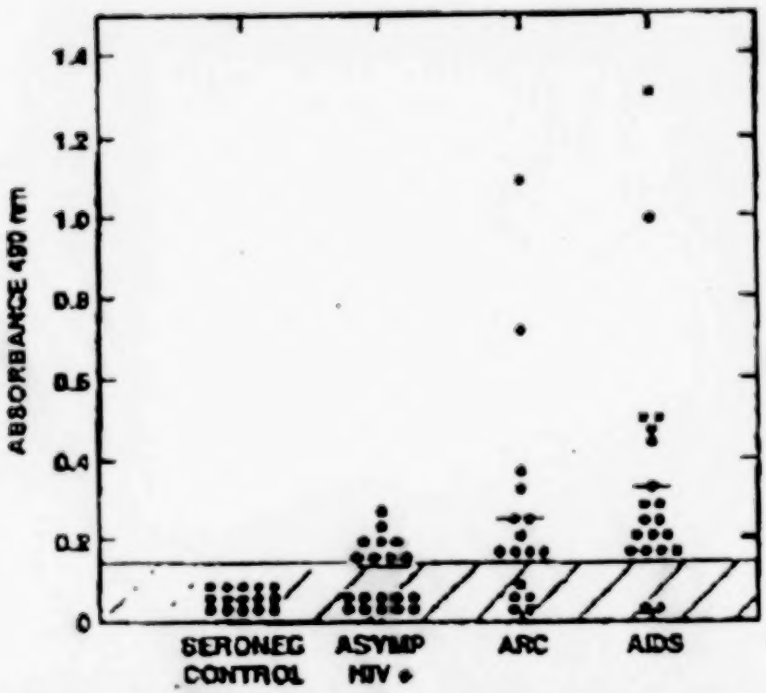

Figure 2. Quantification of human immunodeficiency virus (HIV) RNA in serum based on absorbance in 15 seronegative control subjects and 55 patients in different stages of HIV infection (asymptomatic, AIDS-related complex [ARC], and AIDS). Horizontal bar indicates mean; horizontal line, diagnostic cutoff value.

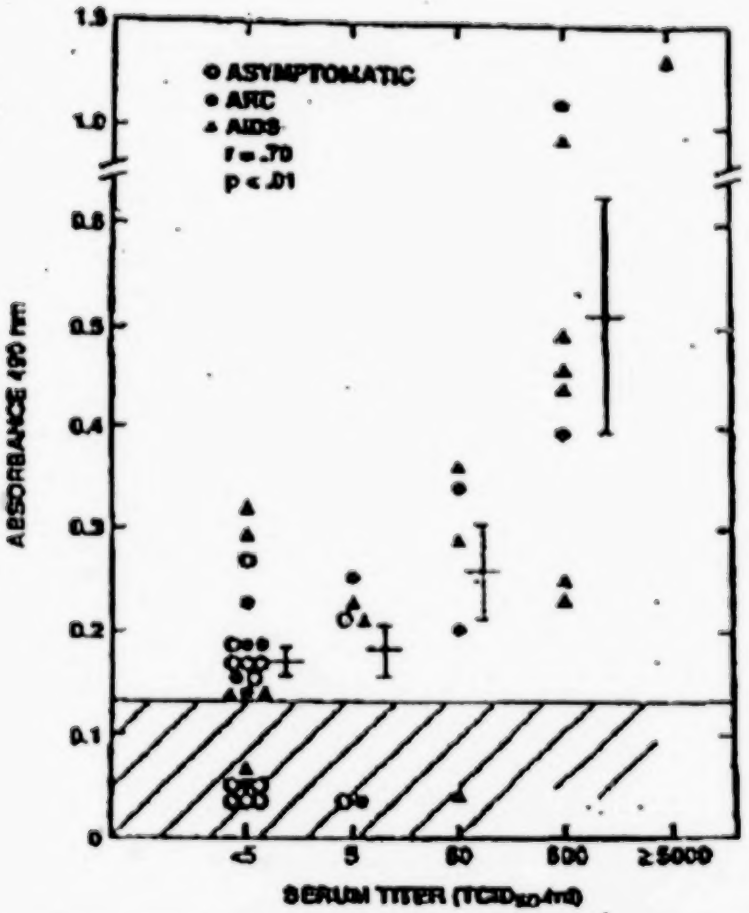

Figure 3. Quantitative serum human immunodeficiency virus (HIV) RNA polymerase chain reaction (PCR) signal in relation to serum HIV infectious titer in 42 patients in different stages of HIV infection (asymptomatic, AIDS-related complex [ARC] and AIDS). Linear regression analysis demonstrated correlation between titer of infectious virus and PCR product absorbance (two-tailed *t* test). Horizontal bar indicates mean and SE; horizontal line, diagnostic cutoff.

test). Serum culture results demonstrated a strong correlation with disease stage: 2 of 13 asymptomatic subjects had positive serum culture compared with 6 of 12 ARC and 12 of 17 AIDS patients.

Surrogate markers of HIV disease progression such as CD4 count and serum p24 antigen level were considered in relationship to PCR measurement of

HIV RNA. Of the 55 sera, 21 were p24 antigen-positive (>70 pg/ml), of which 19 were PCR-positive; 19 of 34 p24 antigen-negative sera were PCR-positive ($P < .007$, Fisher's exact test). However, among the 21 p24 antigen-positive patients, there was no correlation between amount of serum p24 antigen and PCR signal. Serum from patients with <400 CD4 cells/mm^3 was more likely to be PCR-positive: 29 of 37 compared with 9 of 18 sera from patients with >400 CD4 cells/mm^3 ($P < .05$, Fisher's exact test).

Discussion

These results demonstrate that HIV RNA in serum can be detected and quantitated by reverse transcription, PCR, and a nonisotopic enzyme-linked affinity assay. The technique described can be done in 2 days and can detect as few as 10 $TCID_{50}$ of HIV_{IIIB} stock in a small volume of serum, 10 copies of HIV DNA, or 100 copies of cRNA. The observed absorbance values of *gag* gene cRNA copies and infectious HIV_{IIIB} stock demonstrated at least a 10-fold increase in RNA copies in the virus stock compared with the cRNA, suggesting an RNA copy-to-infectious HIV_{IIIB} ratio of 10-100:1. On the basis of reconstruction experiments, quantification of viral RNA may be achieved over a range of 10^2 to 5 X 10^4 copies of input RNA, with a linear range for cRNA of 10^3 to 5 x 10^4. Although an absorbance of $\geq$0.135 would be considered positive in this assay, the ability to quantitate copy number at absorbances of <0.2 would be difficult. This is also true for copy numbers with an absorbance of $\geq$1.5. Thus, only qualitative results can be reliably achieved above and below those absorbances.

The level of sensitivity achieved with respect to the ability of the enzyme-linked affinity assay to detect PCR product from 10 copies of input DNA and 100 copies of RNA is consistent with previously published results. Studies using 30 cycles of amplification of an HIV-specific sequence and hybridization with an isotopically labeled probe have reported the ability to detect as little as 3–5 copies of input DNA [12, 13]. After 30 cycles of amplification, 10 copies of input DNA could be detected in a nonisotopic enzyme immunoassay with probe hybridization [14]. PCR has also been used for quantification of input RNA. By use of an isotopic detection system and 30 cycles of amplification, 100 copies of input mRNA could be detected [15].

Overall, there was agreement between serum PCR and culture. However, three sera were culture-positive and PCR-negative. These negative PCR results were obtained in sera that had ≤ 50 $TCID_{50}$/ml as determined by culture. Because the PCR technique is dependent on the efficiency of extraction of viral RNA from a small volume of serum and the relative efficiencies of the three separate enzymatic reactions, the sensitivity of serum PCR for detection of virus may be limited when a low titer of infectious virus is present in small samples. Ultracentrifugation of larger volumes to concentrate viral particles might improve the sensitivity of the assay. In addition, sensitivity can be enhanced by increasing the number of amplification cycles done or the amount of PCR product assayed in the hybridization reaction (unpublished data).

Serum PCR may increase the sensitivity of quantitative assays of cell-free virus. In 15 sera viral

RNA was detected by PCR while coculture of serum was negative. This could indicate a relatively high proportion of defective or poorly infectious viruses present in some individual sera. Alternatively, this may be an indication of the relative insensitivity of quantitative culture techniques applied to serum. In two recent studies of plasma HIV cultures [1, 2], the sensitivity of this method varied from 100% to 56%. These differences may be related to the clinical stage of disease among patients studied. However, as in the current study using serum, both groups found a higher prevalence or titer of plasma virus in patients with AIDS and ARC compared with asymptomatic patients. Differences in sensitivity between studies of cell-free virus could be related to processing of specimens, culture methods, differences between serum and plasma, or the varying ability among donor lymphocytes from different individuals to support HIV replication in vitro [16]. Comparison of serum and plasma cultures in our laboratory has shown that virus can be recovered somewhat more efficiently from plasma (unpublished data), which may explain the relatively low rate of serum culture positivity (20/42) in this study.

In conclusion, virion HIV RNA was detected and quantitated in the serum of HIV-positive patients by PCR. These findings provide evidence that the amount of cell-free virus in circulation correlates with the presence of HIV infectious titer, serum p24 antigen positivity, CD4 counts $<400/mm^3$, and the presence of HIV-related symptoms. Direct detection of cell-free HIV RNA by PCR is more rapid than quantitative culture and provides a technique independent of cell culture infectivity. Serum PCR may provide an additional marker of disease

progression and drug efficacy that could improve our ability to monitor the course of HIV infection. Further studies will be necessary to validate this approach.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Kozal et al.

Application No.: 07/883,327 — Art Unit: Not Assigned

Filed: May 14, 1992 — Examiner: Not Assigned

For: POLYMERASE CHAIN REACTION ASSAYS FOR MONITORING ANTIVIRAL THERAPY AND MAKING THERAPEUTIC DECISIONS IN THE TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME — Attorney Docket No.: 7627-002

DECLARATION OF BARRY W. ELLEDGE, Ph.D.

Honorable Commissioner of Patents and Trademarks
Box AF
Washington, D.C. 20231

Sir:

I, Barry W. Elledge, Ph.D., do hereby declare the following:

1. I am an associate attorney at the law firm of Pennie & Edmonds. In September, 1992, attorney Laura A. Coruzzi at Pennie & Edmonds requested that I investigate the inventorship issue in the above-referenced application and prepare appropriate documents for filing the correct inventorship with the PTO.

2. In September, 1992, I consulted Dr. Lisa Kole about the inventorship issue. Dr. Kole is a law clerk at the firm of Pennie & Edmonds.

3. Dr. Kole told me that she drafted the above-referenced patent application at the request of attorney Laura Coruzzi. Due to an impending presentation of portions of the subject matter of the application at a scientific meeting, the application needed to be filed by May 14, 1992. Dr. Kole told me that she drafted the application substantially over the two days immediately prior to filing, and the application was reviewed and approved by Dr. Merigan on the same day that it was filed.

4. Dr. Kole further told me that, because of the extreme time pressure under which the application was prepared, she had no opportunity to consult with Dr. Merigan about inventorship prior to filing. Dr. Kole stated that, to the best of her recollection, Dr. Merigan and Dr. Kozal were listed as inventors of the above-referenced application because they were the persons named on the Information Disclosure statement, and with whom she had discussed the invention.

5. In September and October, 1992, I consulted Dr. Merigan and Dr. Holodniy concerning the inventorship question. In November, 1992, I

further consulted Dr. Kozal and Dr. Katzenstein about the same issue.

6. I have examined the Patent Application in light of the written materials supplied to Pennie & Edmonds by Dr. Merigan for preparation of the above-referenced application, including the Invention Disclosure statement by Dr. Merigan and Dr. Kozal, the unpublished manuscript by Dr. Kozal et al., the abstract by Dr. Kozal and Dr. Merigan, and the published journal article by Dr. Holodniy et al..

7. Dr. Holodniy stated that he was until summer of 1991 a research fellow in the Division of Infectious Disease at Stanford University. His inventive contribution to the subject matter of the present application occurred during this period, and principally concerns quantitation of HIV RNA in plasma of AIDS patients.

8. Dr. Katzenstein has indicated that his inventive contribution principally concerns the relationship between the quantity of HIV RNA in plasma of AIDS patients and disease progression.

9. Dr. Kozal has been a postdoctoral research fellow in the Division of Infectious Diseases since approximately the summer of 1991, and his contribution to the present invention began at that time. He indicated that his inventive contribution principally concerns the relationship between the 215 mutation of HIV and disease progression.

10. On the basis of the above materials and conversations, I believe that both Dr. Holodniy and Dr. Katzenstein have made an inventive contribution to the subject matter of one or more claims of the above-referenced application.

11. I further believe that the error in naming the correct inventors arose principally because the extreme time pressure in preparing and filing this application did not permit an inquiry into inventorship prior to the filing date.

12. I also believe that an additional source of the error in naming the correct inventors arose because Drs. Holodniy and Katzenstein made their inventive contributions to different portions of the claimed subject matter and at different times than did Dr. Kozal. Therefore the invention disclosed and claimed in the application includes more than the subject matter of the Invention Disclosure prepared by Drs. Kozal and Merigan.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

/s/ #31,756

Date:
November 16,
1992

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MARK HOLODNIY, M.D.
Acting Chief

Division of Infectious Diseases

In Reply Refer
To: Mail Code

(111-ID)

S. Leslie Misrock
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1155 Avenue of the Americas
New York, NY 10036

Re: Patent application entitled: "Polymerase chain reaction assays for monitoring antiviral therapy and making therapeutic decisions in the treatment of Acquired Immunodeficiency Syndrome"

Dear Mr. Misrock,

I have been asked to comment about the level of my involvement/participation the in patent application entitled: "Polymerase chain reaction assays for monitoring antiviral therapy and making therapeutic decisions in the treatment or Acquired Immunodeficiency Syndrome".

I have been involved in the evolution of this invention since 1988. I have been directly involved in three of the four subsections referred to in the patent

application, most notably those on page 6, section 5, and in particular sections 1, 2 and 4. On page 6, section 5.1 of the patent application, the section beginning "PCR assay of plasma HIV RNA", the description that continues through page 10, line 2, is a body of work published in the Journal of Infectious Diseases in 1991 for which I am the first author. This paper represents one of the first published reports on the detection and quantification of cell-free virion associated HIV RNA in the serum of HIV infected patients. My Involvement in the above referenced project included: obtaining clinical samples, developing the methodology for detection and quantification using PCR techniques, generation and analysis of data, and the writing of the manuscript. In regard to section 5.2, page 10, line 20 of the patent application, the section beginning "PCR assay in peripheral blood mononuclear cells", I was directly involved in developing assays to detect HIV DNA in peripheral blood mononuclear cells. Papers, although not mentioned in the application, demonstrate my involvement in PCR assays of peripheral blood mononuclear cells. Both Clarke, Holodniy, et al (1992) Journal of Acquired Immune Deficiency Syndrome, and Holodniy, et al (1992) Biotechniques, illustrate the techniques of PCR assays of peripheral blood mononuclear cells that were developed in the laboratory. My other major contribution to this invention is referred to in section 6 of the patent application which begins on page 18 and ends on page 30. This section outlines work which demonstrates a reduction in plasma HIV RNA after dideoxynucleoside therapy is determined by the polymerase chain reaction. This project was published in the Journal of Clinical Investigation

(1991), Holodniy, et al. This work is crucial to the invention because it demonstrates the utility of using plasma HIV RNA as a marker for antiretroviral therapy. My participation in this project involved: collection of samples, execution of experiments, analysis of data, statistical analysis, and writing of the manuscript. Therefore my participation in the conception of this invention revolves around claim numbers 9, 14, and 19. I hope this letter accurately represent the level of my participation in this invention. If you have any questions, don't hesitate to contact me.

Sincerely,

/s/

Mark Holodniy, M.D.

SUPPLEMENTAL APPENDIX

Supreme Court, U.S.
FILED
DEC 16 2010
OFFICE OF THE CLERK

No. 09-1159

IN THE

Supreme Court of the United States

BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY,

Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

SUPPLEMENTAL JOINT APPENDIX

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PETITION FOR CERTIORARI FILED MARCH 22, 2010
CERTIORARI GRANTED NOVEMBER 1, 2010

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NOTEBOOK NO. 3702

ISSUED TO CLAYTON CASIPIT

ON JUNE 19 19 89

DEPARTMENT MICROBIAL GENETICS

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* * *

Project No. NTID

134 Book No. 3702 TITLE DOR Activity Study of Standard

From Page No.

Discussion:

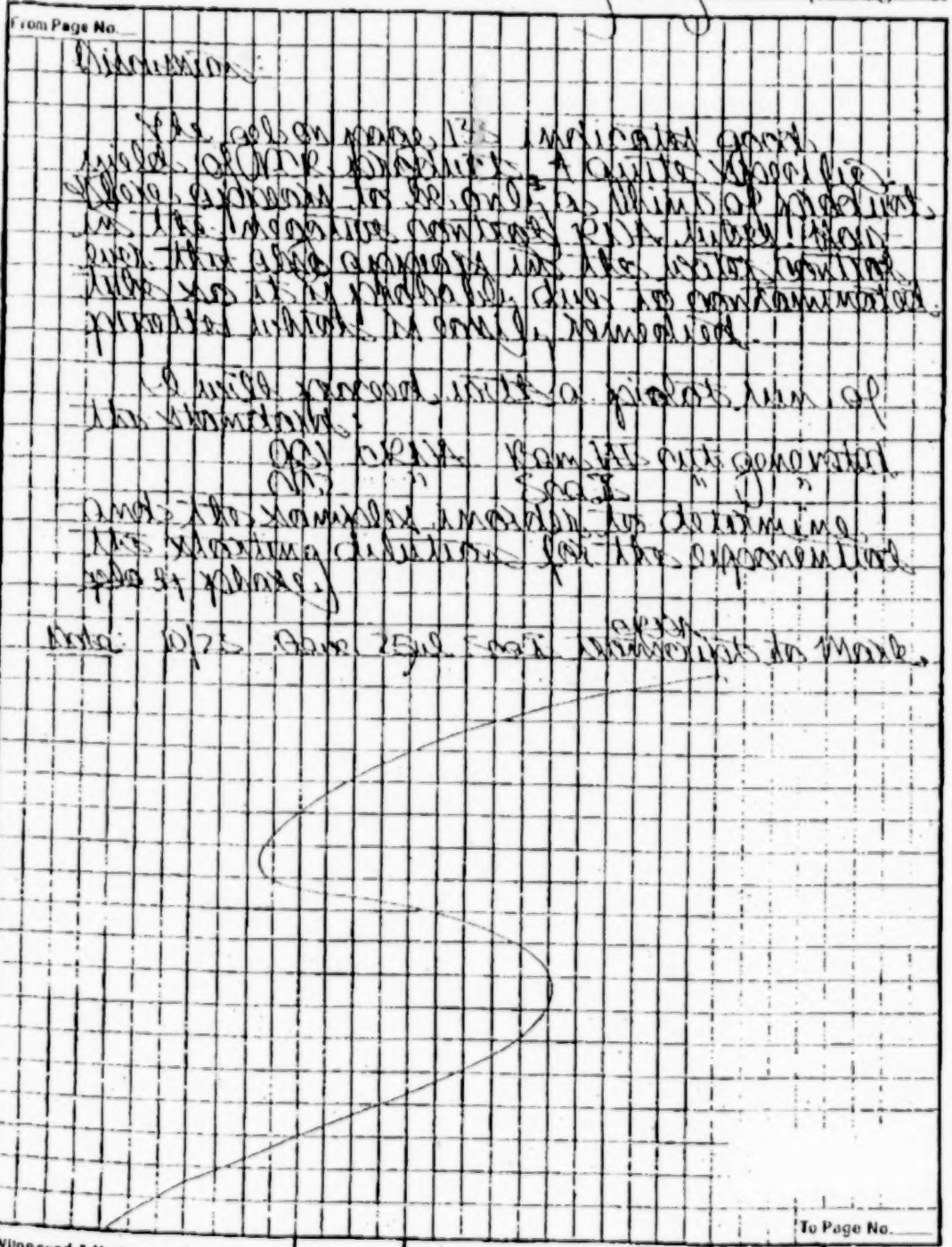
The gels on page 133 indicate good yield of DOR product. A quite specific. There appears to be only a thing of product in the negative control RNA tube. However that also appears in the water control tube so it is probably due to contaminated pipettes which is easily remedied.

I will proceed with a pilot run of the standard:

OC1 CRNA Ram HI cut generated
OC2 " Sca I " "

and the samples in order to determine the starting dilution for the exponential phase.

Note: 10/25 Gave 25µl Sca I transcripts to Mark.



To Page No.

Witnessed & Understood by me	Date	Invented by	Date
Walter J. Gosier	10-30-89	Recorded by C. Gosier	10/20/89

Confidential

* * *

LABORATORY NOTEBOOK

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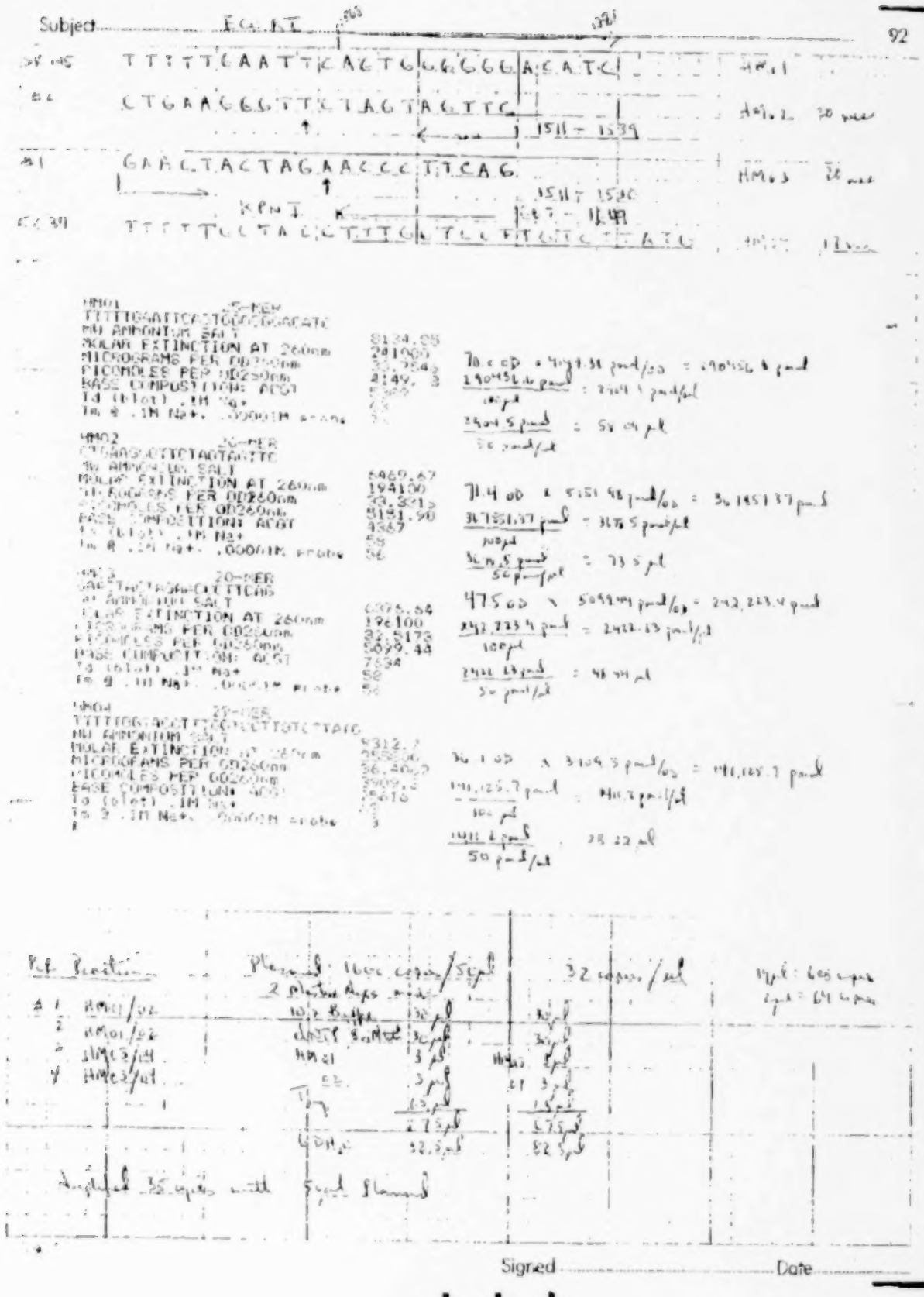
* * *

STAN 016001



Subject 92

Signed ..... Date .....

* * *

BEST AVAILABLE COPY

Rosenbach

FAST AND EASY RNA ISOLATION FOR THE CLINIC

1. Ficoll-hypaque 1-2 mls of blood. Remove PBL band to a 4 ml tube. A 2 ml microfuge tube is OK.

2. Dilute with ice-cold PBS and pellet at 500 X g for 5 min. Wash 1X with ice-cold PBS.

3. Resuspend PBLs in 200-400 ul of ice-cold IHB/0.5% NP-40 containing fresh 0.01% DEP. Transfer cells to a microfuge tube.

4. Vortex cells and pellet nuclei (5-10 sec) in a microfuge. Save nuclei for DNA preparation if desired.

5. Transfer post-nuclear supernatant to another microfuge tube and place in a humidified 37°C H20 bath for 20-30 min, then 10-20 min in a humidified 70°C H20 bath, then back to 37°C for 20 min. Keep caps loose to allow DEP gases to escape. Screw cap microfuge tubes work well for this.

6. Pellet any precipitate that forms and transfer supernatant to another microfuge tube. Use 5-10 ul of sup for the reverse transcriptase/PCR reactions.

IHB = isotonic high pH buffer = 140mM NaCl, 10mM Tris-Cl and 1.5mM $MgCl_2$, pH 8.0.

DEP = diethylpyrocarbonate (Sigma DEP OK).

Note: If RT/PCR does not work on + control, try warming RNA sample again at 37°C for 30 min. Sometimes there is residual DEP left in the RNA soln.
The "dirty" RNA may not work as well as purified RNA preps. However, by this method it is easy to detect IL-2 mRNA in induced and uninduced PBLs.
We have used this method with 10^5 to 10^7 cells in a vol of 200-400 ul. One million cells is a convenient amount for PBLs. Use fewer tissue culture cells with this method because they have much more RNA/cell. The lowest number of cells that can be used by this method has not been tested. I would just add carrier RNA and keep vols in the 50-100 ul range.

Confidential Material

ELISA PCR Procedure

PROTOCOLS FOR NON-ISOTOPIC PCR

MASTER MIX

SOLUTION	(FOR 20 REACTIONS) VOLUME	(PER PCR REACTION)
10X TAQ Salts	200 µL	
8 mM dNTP (working solution)	200 µL	20 nmol each
BW 16H (biotinylated SK39)	20 µL	60 pmol
SK 39	20 µL	60 pmol
TAQ Polymerase	10 µL	2.5 units
GD H2O	552 µL	

REACTION MIX

SOLUTION	VOLUME
Mineral Oil	50 µL
Master Mix	50 µL
Placental DNA	25 µL
Sample DNA	25 µL

THERMOCYCLER PROGRAM FILE #21

Cycles 1 - 2	95° C 1 min; 55° C 7 min
Cycles 3 - 27	95° C 0.5 min; 65° 2 min
Cycles 28 - 39	95° C 0.5 min; 65° C 7 min

BEAD BLOCKING SOLUTION

	VOLUME
50X Denhardt's	2 mL
5% Gelatin	2 mL
Sheared Herring Sperm DNA	5 mL (50 µg/mL)
DI H20	1 mL

Dilute equal volume of beads with blocking solution. Incubate overnight at 4° C.

PROCEDURE FOR NON-ISOTOPIC DETECTION

DENATURATION

Heat 30 µL PCR sample plus 20 µL 6X SSPE buffer, pH 7.4, at 85° C for 5 minutes. Cool on ice for 10 minutes.

HYBRIDIZATION

ADD 10 µL 50x Denhardt's buffer (to 5X final) and 10 µL HRP-oligonucleotide probe (1 pmol) in 1X Denhardt's to denatured sample. Anneal at 42° C for 1 hour.

CAPTURE

Add 100 µL blocked avidinated 2.54 µ polystyrene beads (~150 pmoles avidine), full #2728BBA to wells on a 96 well 1.2 µ LOPRODYNE membrane bottomed PALL plate. Support plate on a Millipore Vacuum Filtration holder and wash beads 5 times with 200 µL PBS. Release vacuum and add samples to wells and allow the capture reaction to proceed for 20 minutes. Wash the bead-target-oligo probe complex 6X with PBS by resuspending the beads then filtering.

COLORIMETRIC ASSAY

Place a 96 well microfilter plate beneath the LOPRODYNE plate in the vacuum filtration holder.

Add 150 µL of OPD (one 30 mg Sigma tablet) dissolved in 48 mL OPD dilution buffer (50 mM Citrate, pH 5.5 with Urea Peroxide.)

Allow reaction to occur for 10 minutes.

Quench reaction with two 50 µL aliquots of 2N H_2SO_4, filtering after each aliquot.

Read absorbance at 490/405 nM on ELISA plate reader.

100 µl of Reaction into new ELISA plates

M 10^4	10^4
10^3	10^3
10^2	10^2
10	10^1
P	P
1	1
2	2
3	3
4	4
5	5
6	6
7	7
8	8
9	9
10	10
11	11
115	115
116	116
Beads	Beads
OPD	OPD

20 µl of PSH product of [illegible] DNA was added to ELISA assay.
volume difference made up with 5x SSPE buffer.

500 µl 50x Denhardt's

520 µl 1x Denhardt's
500 µl " + 20 µl probe

Date

* * *

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cRNA Internal Standard

Research principal from Alice Ling/Kirsten — 2.3 μg/μl — 10^6 molecules ≡ 584 fg

2.54 μl x 2.3 μg/μl = 5.84 μg — Mol wt = 5.84×10^6 g → 5.84×10^{-13} g

2.54 μl add to 10 ml (10,000 μl)

10 μl add to 1 ml (1000 μl)

10 μl of 1 ml solution = 5.84×10^{-13} g, or 1×10^6 molecules

Add 10 μl (1×10^6 molecules) to 90 μl Diluent tube:

10 μl	10 μl	10 μl	10 μl	10 μl	10 μl	10 μl	10 μl
90 μl Diluent	90	90	90	90	90	90	170
10^5 / 10 μl	10^4 / 10 μl	10^3 / 10 μl	10^2 / 10 μl	10^1 / 10 μl	10^0 / 10 μl	10^{-1} / 10 μl	10^{-2} / 10 μl

Stock Diluent: 1 μg/μl solution of ddH_2O and Yeast tRNA

10 mg Yeast tRNA / 10 ml ddH_2O

Repeat Plasma Sample PCR

When I do a PCR reaction on some days it comes out with the correct band size but not bright and sometimes the signal is lost. I wonder why this is the same sample, the master mix efficiency and see if there is any decay in signal from freeze thawing.

Plate design for Extract

DW =

Extraction data to be recorded digitally

200 μl of vapor source mixed (Anti Shield/ $NaAc$/ Ethanol/ Chloroform/ IPA) 200/20/200/400 μl

Apt	Aptamer 450 μl	Extract 450 μl	1:1 Vol
PP	Shield 200 μl	Extract 200 μl	1:1 Vol
Wash	EtOH 200 μl		

Signed [illegible] Date 11/6/84

* * *

Subject 53

Hybridization 50 sample 5 µl PCR product 45 µl SSPE SA → 95° 5' → Ice

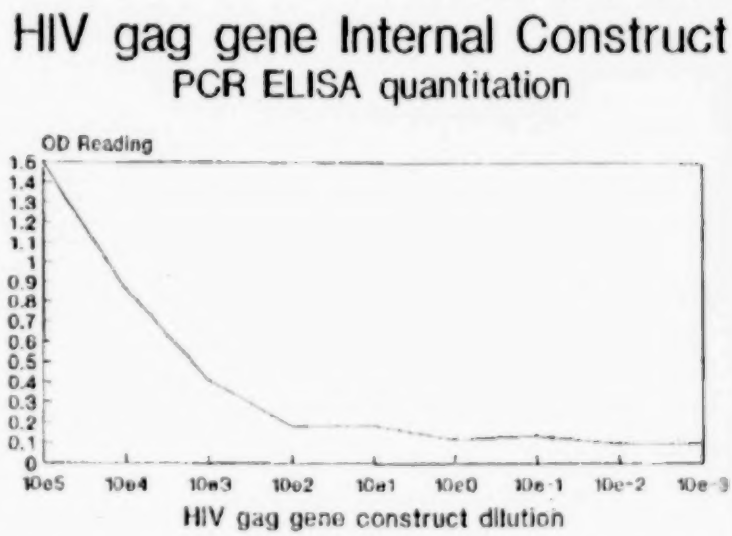
50x Denhardt 500 µl 20 µl added to each Reaction
1 x Denhardt 500 µl
HPP Probe 20 µl 42° for 1°

ELISA performed as Reported before.

	1	2	3	4	5	6	7	8	9	10	11	12	
A													A
B													B
C	1	2	3	4	5	6	7	8	9	10	11	12	C
D	13	14	15	16	17	18	19	20	21	22	23	24	D
E	25	26	27	28	29	30	31	32	33	34	35	36	E
F	37	38	39	40	41	42	43	44	45	46	47	48	F
G													G
H													H

ELISA Results 11/16/89

1	.337	25	.091
2	.361	26	.081
3	.147	27	.096
4	.205	28	.093
5	.120	29	.860
6	.177	30	.411
7	.109	31	.182
8	.131	32	.188
9	.143	33	.121
10	.092	34	.138
11	.101	35	.099
12	.102	36	.101
13	.103	37	.107
14	.102	38	.106
15	.104	39	>1.4
16	.106	40	>1.4
17	.109	41	.189
18	.108	42	.119
19	.102	43	.113
20	.110	44	.094
21	.117	45	.082
22	.114	46	.163 OPD + beads + Probe
23	.103	47	0 OPD + beads
24	.100	48	0 OPD alone



3 Samples of RNA extract directly PCR, no signal above background.

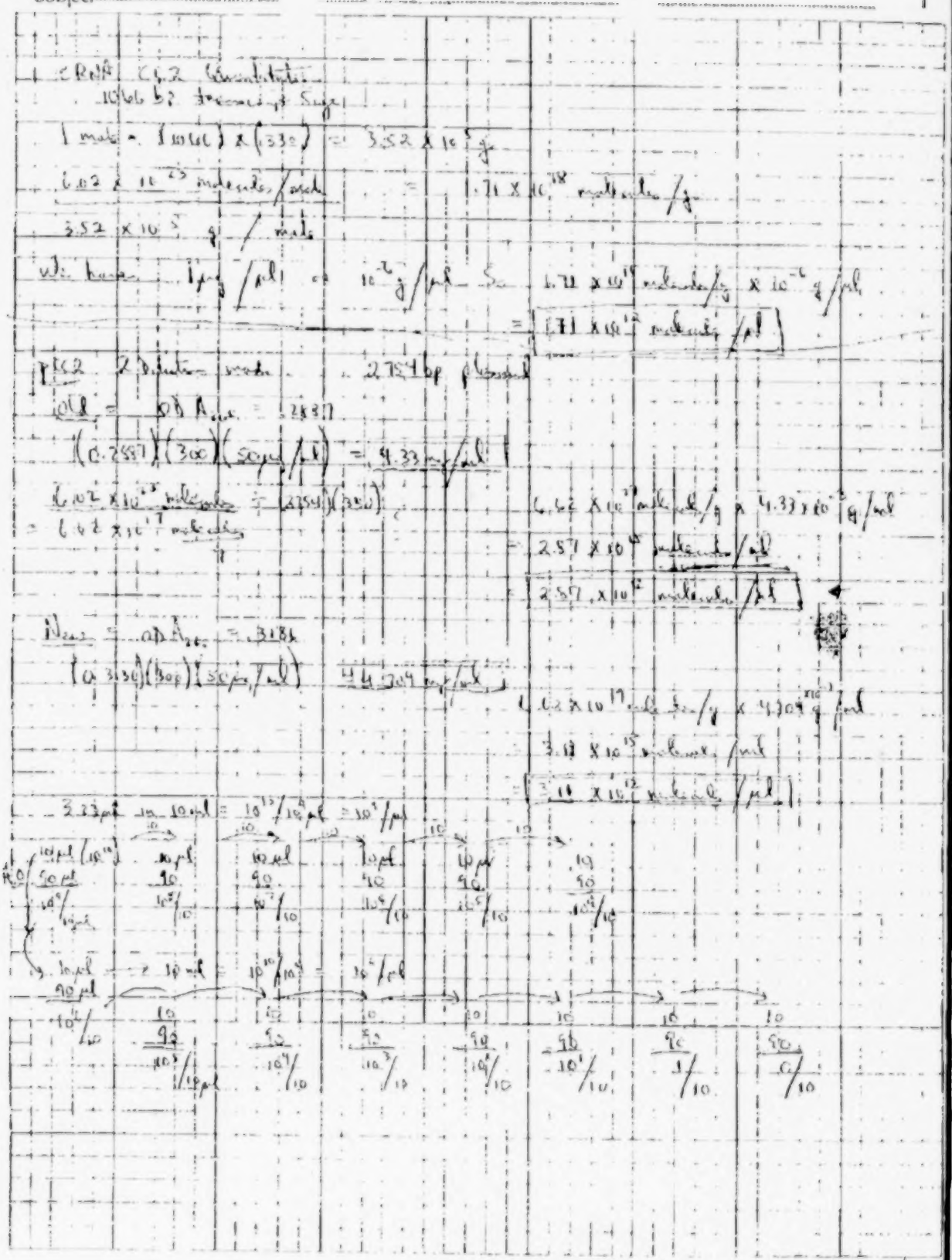
Signed ..... Date 11/16/89

Confidential Material

* * *

STAN 016173

Subject



Signed

Date

Confidential Material

* * *

Subject

6

Page No. 121 12-20-89

Received 60 fluorescine labeled Probe; Keep frozen -20°C
dessicated in vial
20 OD
20 OD X 2647.6 Picomoles per OD 260nM = 52,952 picoMole

```
FL_CC09          32-MER
XATCCTGGGATTAAATAAAATAGTAAGAATGT
MW AMMONIUM SALT                  10108.3
MOLAR EXTINCTION AT 260nm         377700
MICROGRAMS PER OD260nm            26.7623
PICOMOLES PER OD260nm             2647.6 ✓
BASE COMPOSITION: ACGT            14269
MIXED BASES: YRNMKSWHBVDX2        0000000000010
X=FLUORESCEIN
Td (blot) .1M Na+                 60
Tm @ .1M Na+, .000001M probe                    65
$
```

dissolve in TRIS EDTA pH 7.4 buffer (or the buffer we [TE] used for Biotinylated primer)
use 1 pMole per 50λ sample

must dilute so that 10λ contains 1 pMole (final)
A. Dilute to 1 ml TRIS EDTA aliquot & freeze; used TE
= 529.52 pMoles/ml
= 529.52 pMoles/10λ
B. For 1 pMoles/10λ, dilute 1: 529.52
or 1ml: 529.52 mls
or 0.1ml: 52.952 mls
or 10λ: 5.2952 mls

aliquot 100λ and freeze -20°C

SK12 Wild Type - Fluoro
SK13 Constant - Probe

Signed MJ Date 4/12/90

Confidential Material

* * *

STAN 016233

picked up 7-11-90
Stored -20°C
two sets/pl
4652 pl
Cetus DNA primers

```
SIK15          20-MER
GTCTGTTGTGTGACTCTGGT
MW AMMONIUM SALT                    6467.65
MOLAR EXTINCTION AT 260nm           181600
MICROGRAMS PER OD260nm              35.6148
PICOMOLES PER OD260nm               5506.41
BASE COMPOSITION: ACGT              1379
Td (blot) .1M Na+                   60
Tm @ .1M Na+, .000001M probe
$

SIK16          20-MER
GAGGCTTAAGCAGTGGGTTC
MW AMMONIUM SALT                    6519.69
MOLAR EXTINCTION AT 260nm           195800
MICROGRAMS PER OD260nm              33.2977
PICOMOLES PER OD260nm               5107.25
BASE COMPOSITION: ACGT              4385
Td (blot) .1M Na+                   62
Tm @ .1M Na+, .000001M probe
$

SIK17          22-MER
XGGCTTGCTGAAGCGCGCACGGCAAGAGG
MW AMMONIUM SALT                    9147.55
MOLAR EXTINCTION AT 260nm           348300
MICROGRAMS PER OD260nm              29.6709
PICOMOLES PER OD260nm               3243.52
BASE COMPOSITION: ACGT              67123
MIXED BASES: YRNMKSWHBVDXZ          0000000000010
X=BIOTIN
Td (blot) .1M Na+                   75
Tm @ .1M Na+, .000001M probe
$

SIK18          28-MER
GCCAAGGATCCGTTCACTAATCGAATGG
MW AMMONIUM SALT                    9040.52
MOLAR EXTINCTION AT 260nm           273900
MICROGRAMS PER OD260nm              33.0066
PICOMOLES PER OD260nm               3650.97
BASE COMPOSITION: ACGT              8776
Td (blot) .1M Na+                   68
Tm @ .1M Na+, .000001M probe
$

SIK19          24-MER
ZGGTGTCGACATAGCAGAATAGGC
MW AMMONIUM SALT                    7495.4
MOLAR EXTINCTION AT 260nm           264200
MICROGRAMS PER OD260nm              28.3702
PICOMOLES PER OD260nm               3785.01
BASE COMPOSITION: ACGT              7404
MIXED BASES: YRNMKSWHBVDXZ          0000000000001
Z=HRP
Td (blot) .1M Na+                   65
Tm @ .1M Na+, .000001M probe
DEFINE Z
?
HRP

SIK20          21-MER
ZCTTAGGCATCTCCTATGGCA
MW AMMONIUM SALT                    6374.62
MOLAR EXTINCTION AT 260nm           204200
MICROGRAMS PER OD260nm              31.2175
PICOMOLES PER OD260nm               4897.16
BASE COMPOSITION: ACGT              4646
MIXED BASES: YRNMKSWHBVDXZ          0000000000001
Z=HRP
Td (blot) .1M Na+                   61
Tm @ .1M Na+, .000001M probe
DEFINE Z
?

SIK21          30-MER
ZGAAGAAGCGGAGACAGCGACGAAGAGCTC
MW AMMONIUM SALT                    9503.93
MOLAR EXTINCTION AT 260nm           349000
MICROGRAMS PER OD260nm              27.2316
PICOMOLES PER OD260nm               2865.33
BASE COMPOSITION: ACGT              116111
MIXED BASES: YRNMKSWHBVDXZ          0000000000001
Z=HRP
Td (blot) .1M Na+                   71
Tm @ .1M Na+, .000001M probe
DEFINE Z
?
```

9.8 OD

= 29,511 pmol

Stock in 118 µl

= 250 pmol/µl

87

19.5 OD

19.5 x 36.50 = 711.75 pmol

Stock in 284 µl

= 250 pmol/µl

77

Tm

4.72 OD

1:47

.11

1:11

7.9

1:24

Signed

Date

* * *

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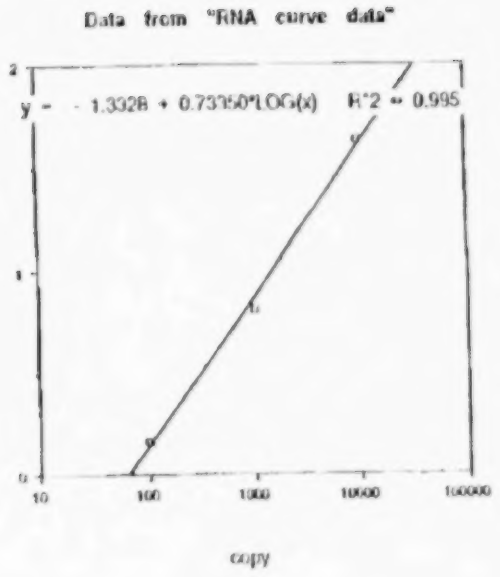
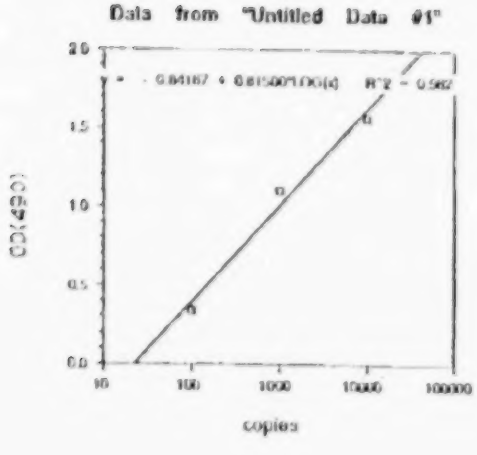
Subject 53



RNA curves from experiments for Gen Statistical Study -



Signed ..... Date .....

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Subject 54

Pre/Post T 2 pre breaches and 1/2 months p
Expected as before.

4/17/91

76	[illegible]			17		[illegible]			
	[illegible]			18		[illegible]			
	[illegible]			19		[illegible]			
	3/8			20		[illegible]			
	[illegible]			21		[illegible]			
	[illegible]			22		[illegible]			
	[illegible]			23		[illegible]			
	[illegible]			24		[illegible]			
Redacted	[illegible]			25	Redacted	[illegible]			
	[illegible]			26		[illegible]			
	[illegible]			27		[illegible]			
	[illegible]			28		[illegible]			
	[illegible]			29		[illegible]			
	[illegible]			30		[illegible]			
	[illegible]			31		[illegible]			
	[illegible]			32		[illegible]			

4/18/91

LT Tech 2 — 32 patient samples

3 [illegible] controls

LT [illegible]

Mate from 40 x 10 = 400 µl

[illegible]	50
[illegible]	40
[illegible]	40
[illegible]	20
LT	40
	220
H_2O	180

33 - 35 $10^4 - 10^2$

36 [illegible]

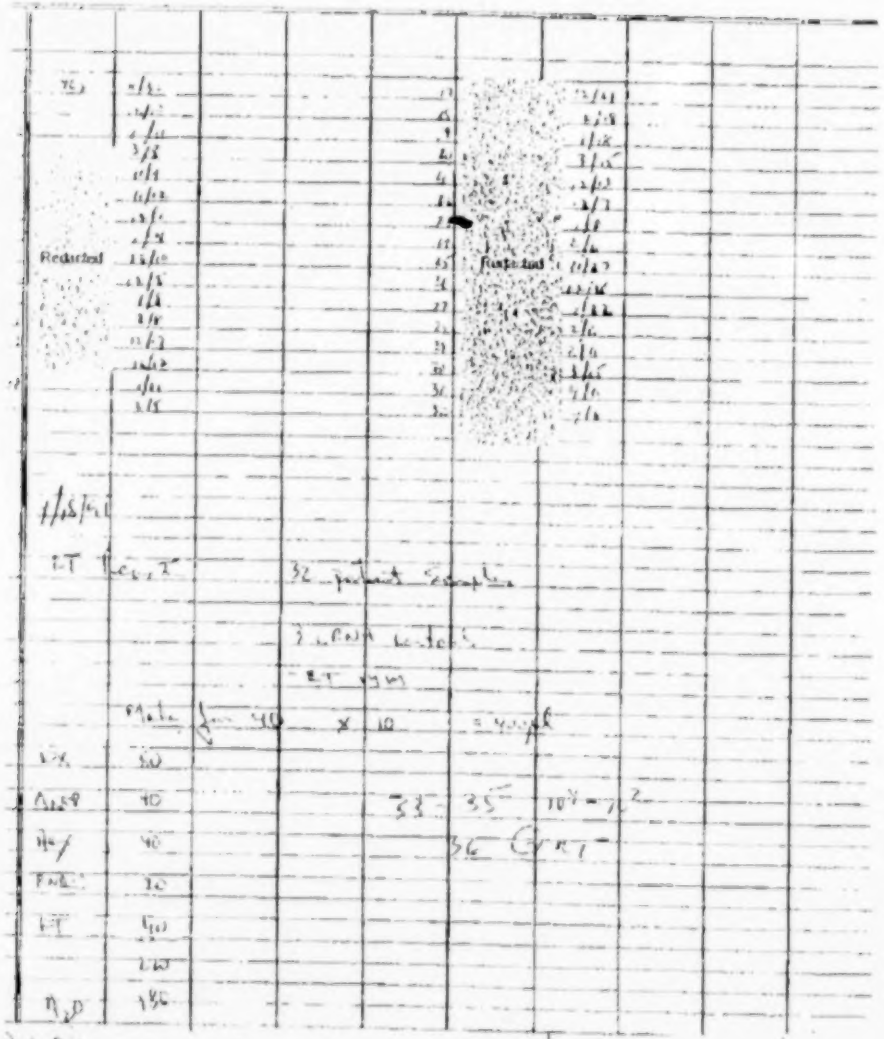
PCR Rxn — 35 samples — 42 x 80 = 3360 µl

10 x	420
3 [illegible]	42
39	42
dpnt	42
[illegible]	21
	567

H_2O 2793

[illegible] Extracts

Signed [illegible] Date 4/17/91



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RECEIVED
JAN 10 1990
PATENT DEPARTMENT

1/9/90

INVENTION DISCLOSURE

For IPLD Use Only

Date: _____
Patent ID # CE-90-003
Patent Com: 102

To: REDACTED
From: M. Konrad (for Mark Holodny)

I. DESCRIPTIVE TITLE: Quantitation of HIV-1 viral RNA in human sesum utilizing an in vitro generated internal standard for coamplification and an enzyme linked affinity assay for detection

II. BRIEF SUMMARY What is the invention? What is the problem being solved? How does the invention advance the field beyond what is known in the art? What is surprising? Provide details on process steps, components, results, etc in accompanying pages and use additional pages for the summary if needed

HIV-1 viral particle in HIV-1 infected human sesum undergo a selective extraction procedure for RNA. The resulting viral RNA is coincidence transcribed with an in vitro generated internal standard. The internal standard was constructed utilizing PCR technology and a Rsa I site was deleted in a highly conserved sequence of the pol gene. The cDNA undergoes amplification with a biotinylated upstream primer. The resultant PCR products are separated by Rsa I restriction enzyme digestion on acrylamide gel. The bands excised and counted for radioactive incorporation. Alternatively products are detected by a nonisotopic enzymelinked affinity assay with a colorimetric reaction. Based on optical density reading the sample copy number can be determined.

III. CETUS SCIENTISTS/CONSULTANTS WHO COULD EVALUATE THIS DISCLOSURE ARE

SIGNATURE OF SUBMITTER(S)		SIGNATURE OF WITNESS (ES)	
Mark Holodny	1/9/90	Michael Konrad	1/9/90
Full First Name Initial Last Name	Date		Date
Full First Name Initial Last Name	Date		Date
Full First Name Initial Last Name	Date		Date
Full First Name Initial Last Name	Date		Date

506678

"OUTSIDE COUNSEL'S EYES ONLY"

Δ π EXHIBIT 34
Deponent Holodny
Date 7/19/00 Rpt. SFB
www.oriusoon.com

RMS 00542
CONFIDENTIAL

IV. REFERENCES

A. Lab Notebook(s) Personal lab book

B. Progress Reports (etc.)

C. Relevant Literature and Patent References

V. WHEN DID YOU START WORKING ON THE INVENTION? 9/89

WRITTEN RECORD DATES? ✓

DISCLOSURE TO OTHERS None
(To Whom/Date)

VI. WERE CELL LINES OR PLASMIDS USED IN THE COURSE OF THE INVENTION? IF SO, WHICH? C537 / U1 cell lines pCC2 plasmid

HAVE DEPOSITS BEEN MADE IN CMCC/CTCC? Yes pCC2

VII. DISCLOSURE TO THIRD PARTIES (Publications, field test, commercial use or sale, samples sent to others? When? Please keep IPLD informed of potential disclosures after filing this form.) Abstract submitted to UCLA symposium for molecular and cellular biology

THE INVENTION DESCRIBED ABOVE IS SUBMITTED PURSUANT TO MY "EMPLOYMENT INVENTION AND CONFIDENTIAL INFORMATION AGREEMENT".

506679

"OUTSIDE COUNSEL'S EYES ONLY"

RMS 00543
CONFIDENTIAL

QUANTITATION OF HIV-1 RNA IN SERUM AND CORRELATION WITH DISEASE STATUS USING THE POLYMERASE CHAIN REACTION. Mark Holodniy, David A. Katzenstein, Sohini Sengupta, Alice Wang*, Clayton Casper, David H. Schwartz, Mike Konrad*, Eric Groves* and Thomas C. Merigan, Division of Infectious Diseases, Stanford University School of Medicine, Stanford, CA. 94305, *Cetus Corporation, Emeryville, CA 94608.

The amount of HIV-1 present in serum may be a potential marker in HIV related disease. A method that detects and quantifies HIV-1 viral RNA in serum is presented. To detect HIV-1 RNA, sera was extracted by a guanadinium thiocyanate method, reverse transcribed with MLV reverse transcriptase and amplified by the polymerase chain reaction using a gag gene primer pair (SK38/39) including a biotin labelled upstream primer. The biotinylated PCR product was liquid hybridized to a horseradish peroxidase conjugated probe, bound to avidin, and quantitated from the optical density of a colorimetric reaction.

Reverse transcription and amplification of known amounts of gag gene RNA and infectious HIV_{BB} virus yielded a log-linear relationship between optical density and 10^3 and 10^5 copies of gag RNA and $TCID_{50}$ of virus respectively. No HIV viral RNA was detected in the serum of 5 seronegative healthy controls. In HIV infected patients who were not receiving therapy, serum HIV-1 RNA was detected in 0/5 asymptomatic, 4/5 ARC and 4/5 AIDS patients with copy numbers ranging from 10^3-10^5/200ul of serum. Ultracentrifugation of patient sera revealed detectable signal in pellets, but not supernatant, indicating that signal is attributable to viral RNA. In addition, extracted material was directly amplified for the presence of viral DNA and gave no detectable signal.

We have demonstrated that HIV-1 viral RNA can be detected and quantitated in patient serum over a four log range. An RNA gag gene sequence was used to quantitate viral copy number. In addition, a nonisotopic enzyme linked affinity assay in a microtiter plate system allows easy PCR product detection and quantitation. Quantitation of HIV-1 viral RNA in serum by PCR may be a useful marker for disease progression or monitoring antiviral therapy.

12-22-93

Here is the final copy of the
Abstract submitted with all the names.
Now I have given you a copy of the
title I sent it to you by fax.
I will have the list of patient samples
from the 11-2 NIH study when we
come over next week.

Mark

Copy to
Swiss
Kwok
Kwok
Wong
Cosgrove
SLL
Raymond
JSP
Parker

REDACTED

506680

"OUTSIDE COUNSEL'S EYES ONLY"

RMS 00544
CONFIDENTIAL

17 US005968730A

United States Patent [19]

Merigan et al.

[11] Patent Number: 5,968,730

[45] Date of Patent: Oct. 19, 1999

[54] **POLYMERASE CHAIN REACTION ASSAYS FOR MONITORING ANTIVIRAL THERAPY AND MAKING THERAPEUTIC DECISIONS IN THE TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME**

[75] Inventors: **Thomas C. Merigan**, Portola Valley; **David A. Katzenstein**, Menlo Park; **Mark Holodniy**, Mountain View, all of Calif.

[73] Assignee: **Leland Stanford Junior University**, Palo Alto, Calif.

[21] Appl. No.: **08/470,885**

[22] Filed: **Jun. 6, 1995**

Related U.S. Application Data

[62] Division of application No. 07/884,327, May 14, 1992, abandoned.

[51] **Int. Cl.**[6] **C12Q 1/68**

[52] **U.S. Cl.** **435/5**; 435/6; 436/501; 436/63; 514/44; 536/23.1; 536/24.1; 536/24.3; 536/24.31; 536/24.32; 536/24.33; 935/77; 935/78

[58] **Field of Search** 435/5, 6, 810; 436/501, 63; 514/44; 536/23.1, 24.1, 24.3, 24.33; 935/77, 78

[56] **References Cited**

U.S. PATENT DOCUMENTS

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Ohmann et al. (1991) Journal of Virological Methods, vol. 31, pp. 273–284.

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Holodniy et al, "Quantitation of HIV-1 RNA in the Serum of ARC and Aids Patients Using the Polymerase Chain Reaction (PCR)", Abstract presented at the Sixth International Conference on AIDS, San Francisco, California, Jun. 22, 1990.

Holodniy et al., "Quantitation of HIV-RNA in Serum and Correlation with Disease Status Using the Polymerase Chain Reaction (PCR)", *Journal of Cellular Biochemistry*, Supplement 14D, 1990, Abstract of UCLA Symposia on Molecular and Cellular Biology, Mar. 11-Apr. 6, 1990.

Winters, et al., "Rapid Detection of HIV Infectivity and Measurement of Antiviral Activity Using the Polymerase Chain Reaction (PCR)", *Journal of Cellular Biochemistry*, Supplement 15L, 1991, Abstract of Keystone Symposia on Molecular and Cellular Biology, Mar. 8-Mar. 26, 1991.

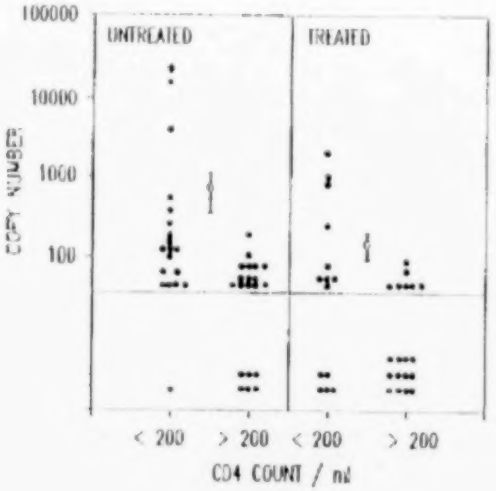
Primary Examiner—Ardin H. Marschel

Attorney, Agent, or Firm—Pennie & Edmonds LLP

[57] **ABSTRACT**

The present invention relates to methods of monitoring, via polymerase chain reaction, the clinical progression of human immunodeficiency virus infection and its response to antiretroviral therapy. According to the invention, polymerase chain reaction assays may be used to predict immunological decline and to identify, at an early stage, patients whose infection has become resistant to a particular antiretroviral drug regimen.

23 Claims, 9 Drawing Sheets



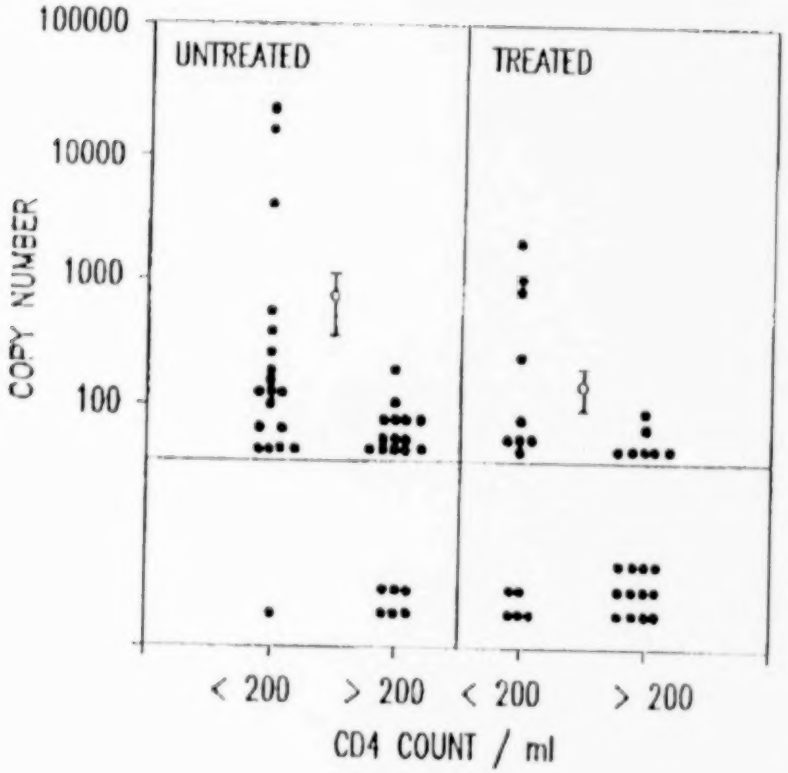

100000
10000
1000
100
COPY NUMBER
UNTREATED
TREATED
< 200
> 200
< 200
> 200
CD4 COUNT / ml

FIG.1

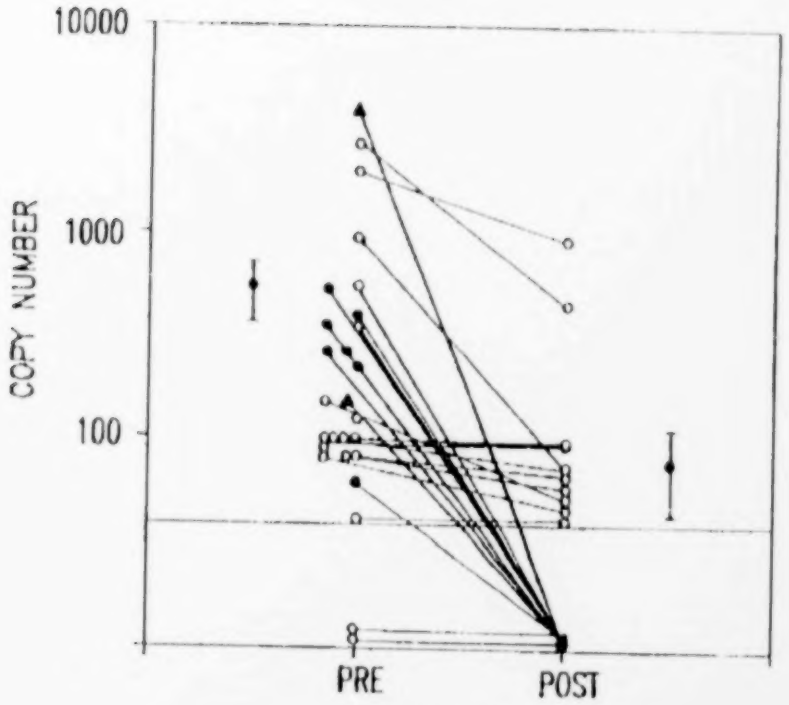

10000
1000
100
COPY NUMBER
PRE
POST

FIG.2

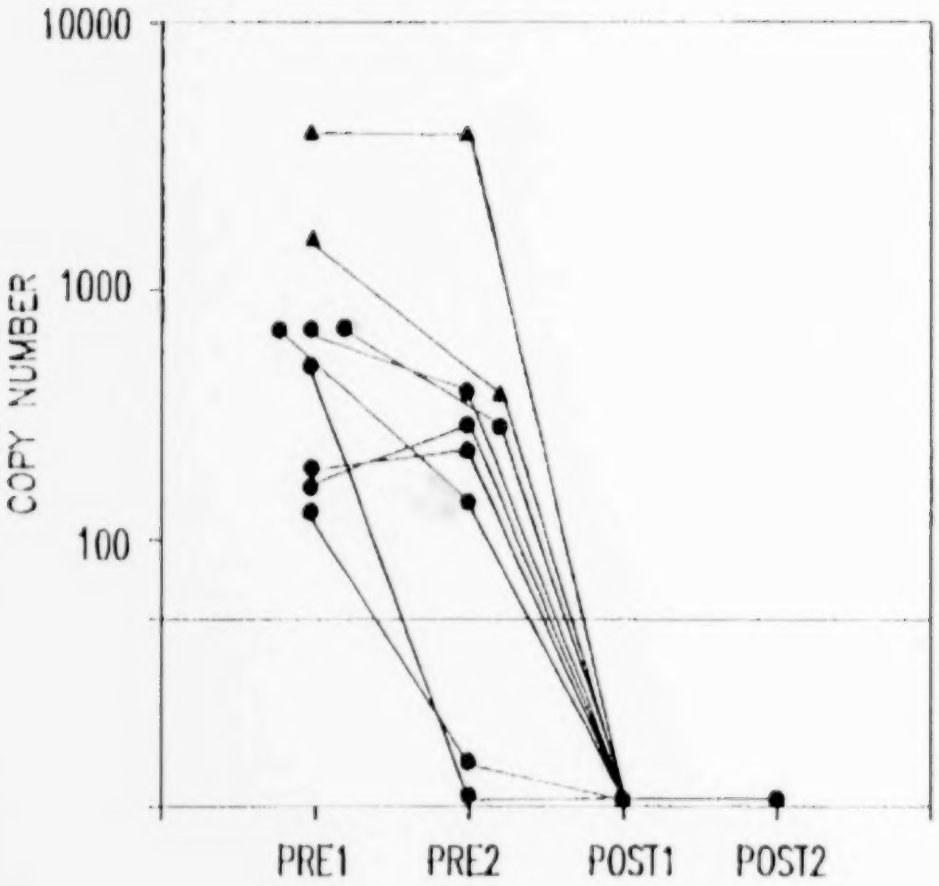


FIG.3

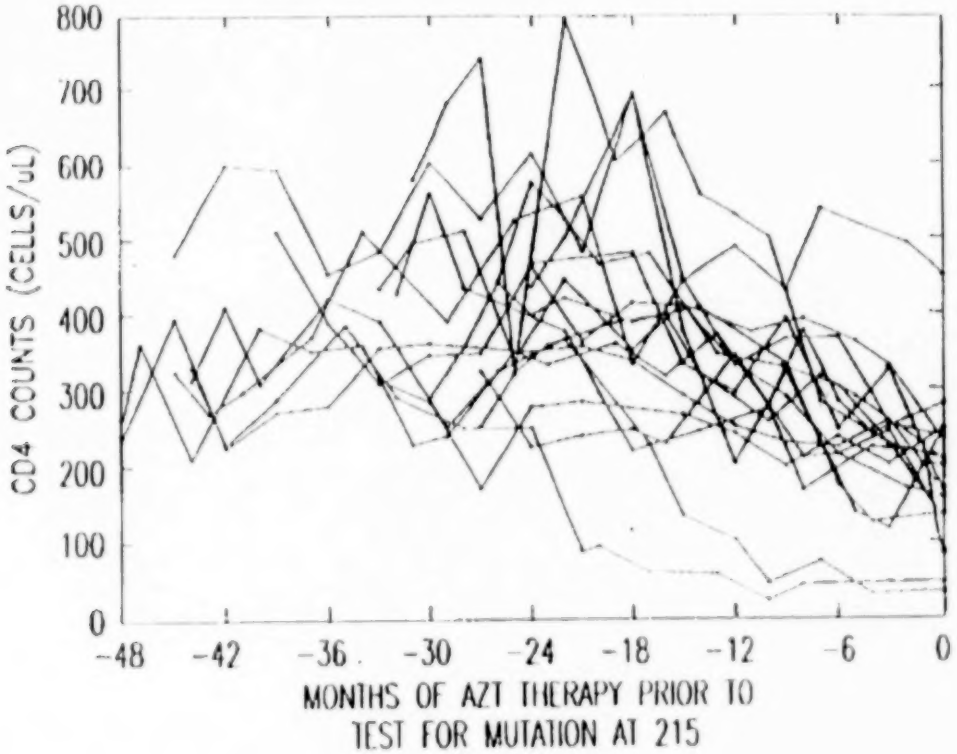

800
700
600
500
400
300
200
100
0
CD4 COUNTS (CELLS/uL)
-48
-42
-36
-30
-24
-18
-12
-6
0
MONTHS OF AZT THERAPY PRIOR TO
TEST FOR MUTATION AT 215

FIG.4A

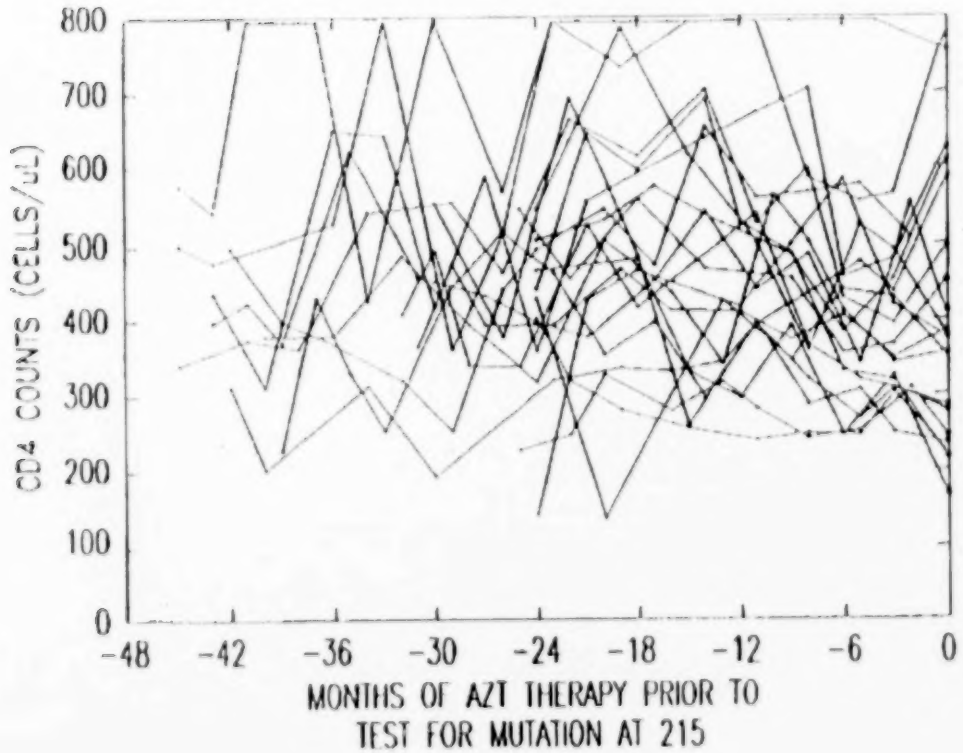

800
700
600
500
400
300
200
100
0
CD4 COUNTS (CELLS/uL)
-48
-42
-36
-30
-24
-18
-12
-6
0
MONTHS OF AZT THERAPY PRIOR TO
TEST FOR MUTATION AT 215

FIG.4B

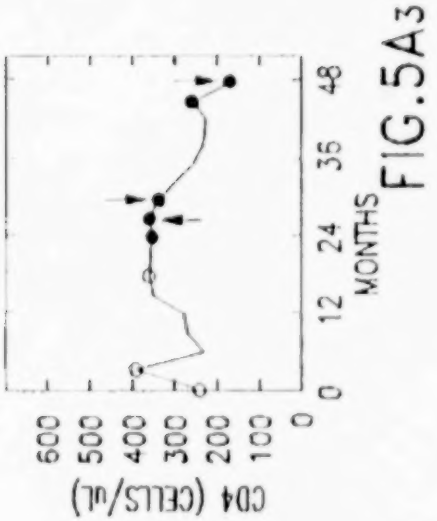


FIG.5A3

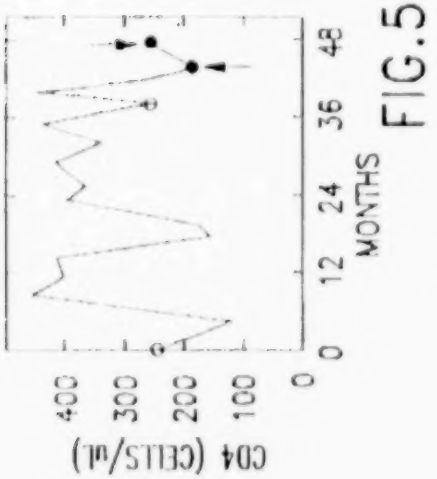


FIG.5A2

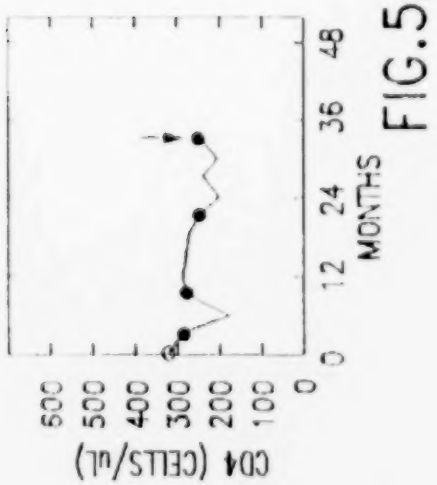


FIG.5A1

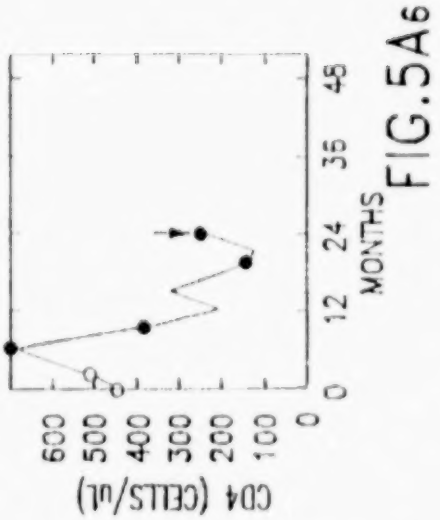


FIG.5A6

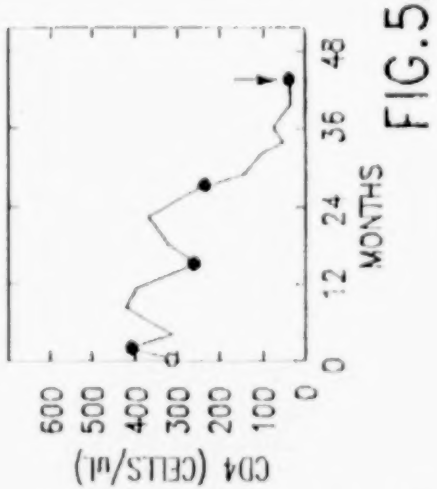


FIG.5A5

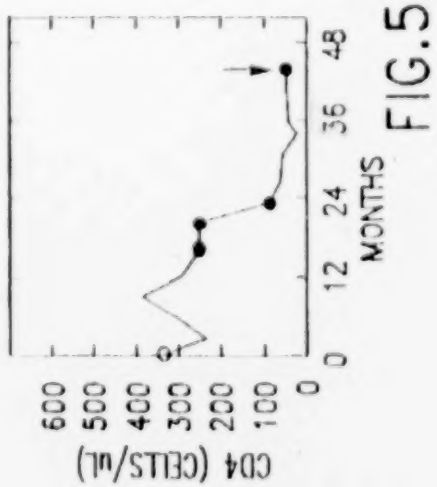


FIG.5A4

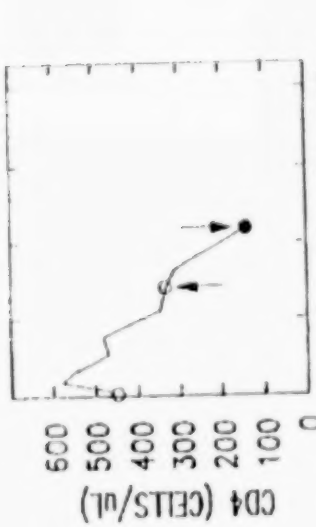


FIG.5A9

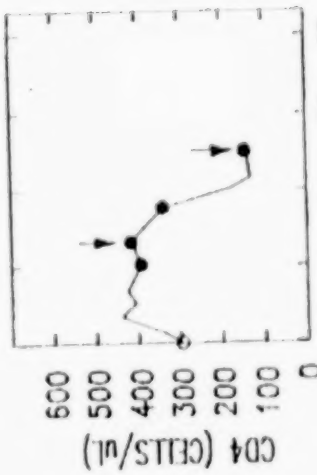


FIG.5A12

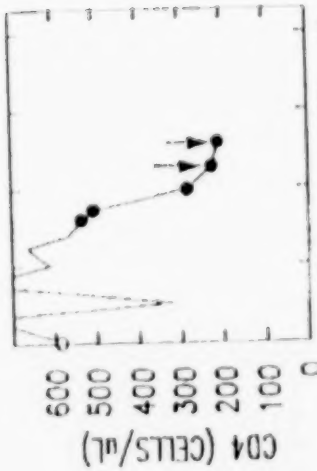


FIG.5A8

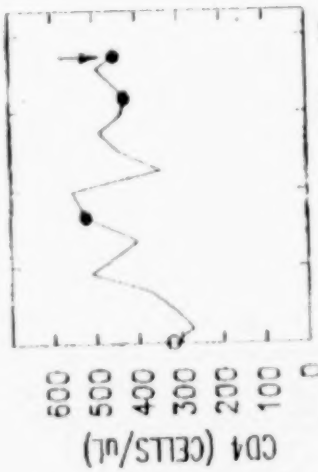


FIG.5A11

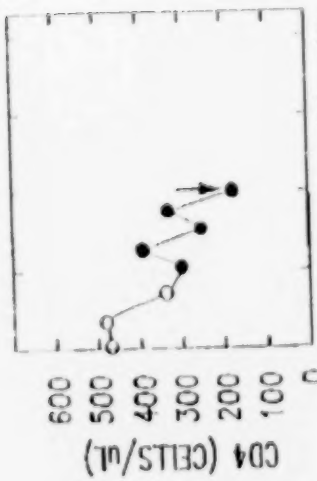


FIG.5A7

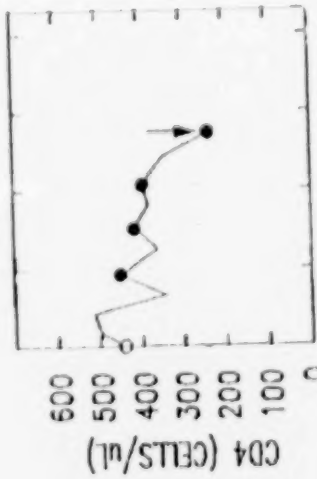


FIG.5A10

FIG.5A15

FIG.5A14

FIG.5A13

FIG.5A16

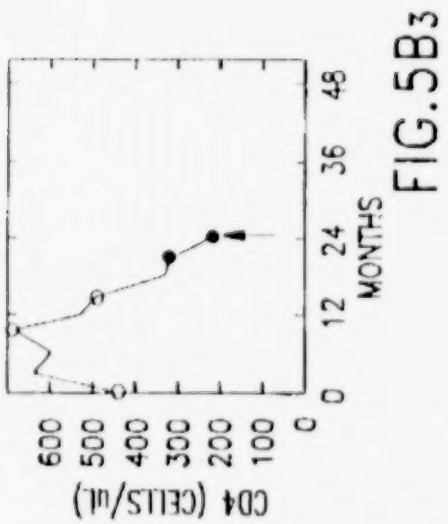


FIG.5B3

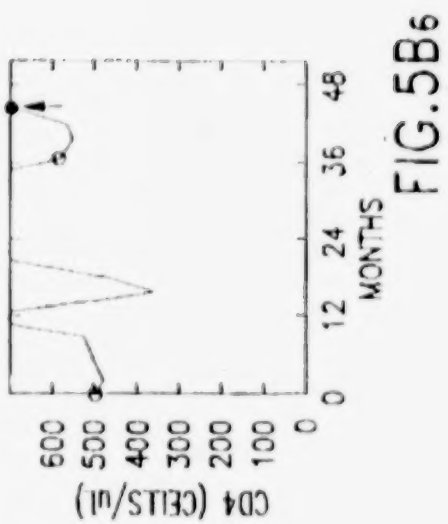


FIG.5B6

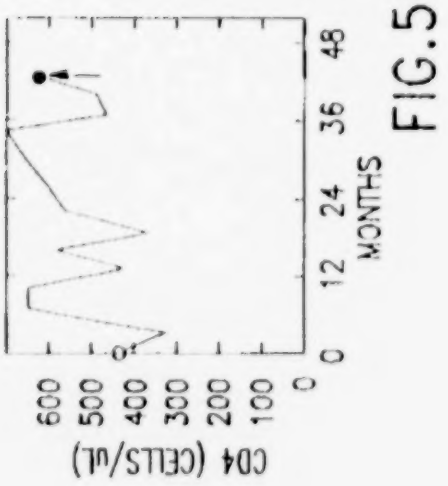


FIG.5B2

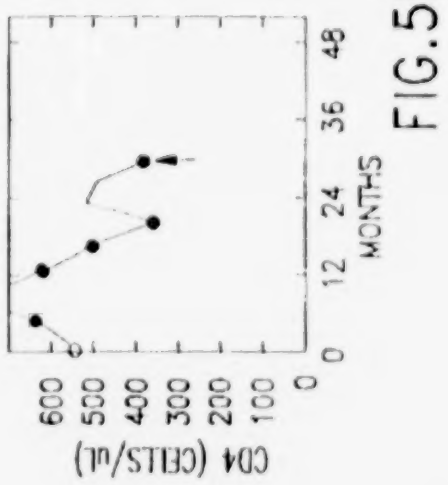


FIG.5B5

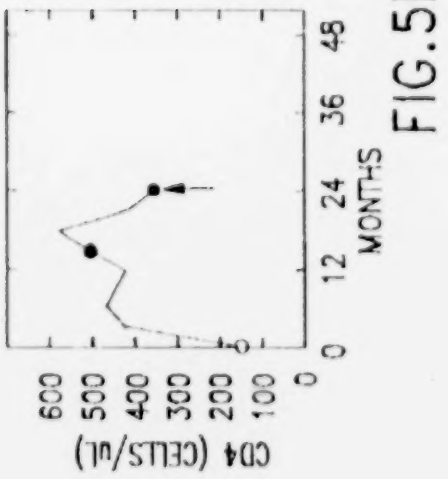


FIG.5B1

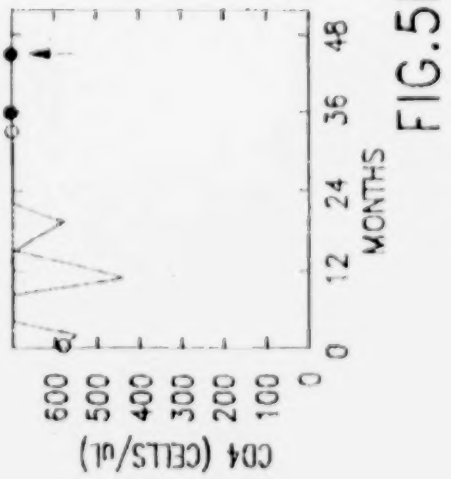


FIG.5B4

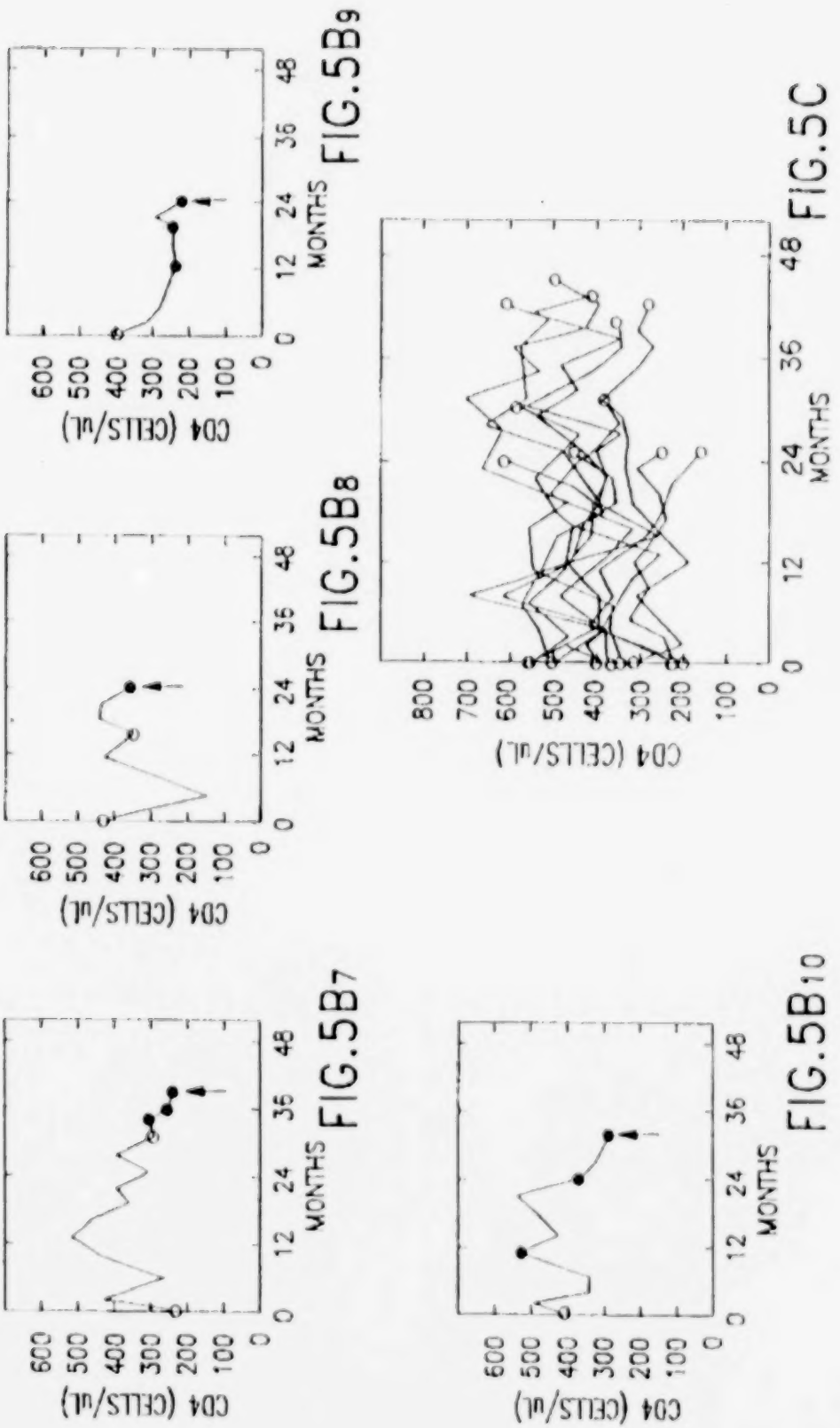


FIG.5B9

FIG.5B8

FIG.5C

FIG.5B7

FIG.5B10

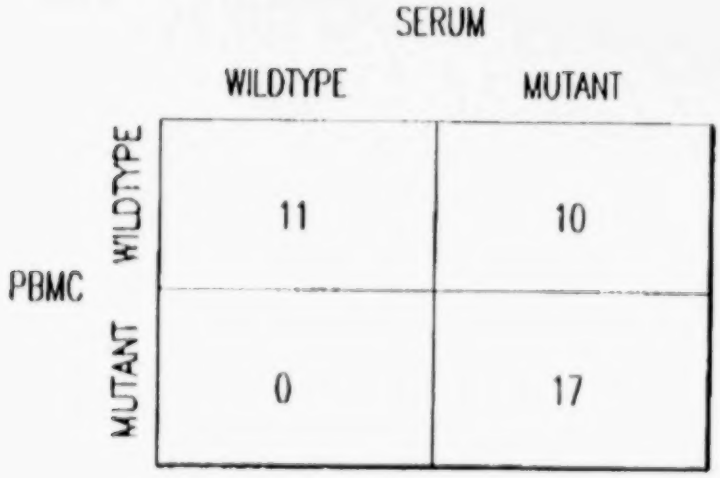


FIG.6

HIV 1
gag (p24) CORE PROTEIN

NAME OLIGO 1
SK 38 5'-ATA ATC CAC CTA TCC CAG TAG GAG AAAT

OLIGO 2
SK 39 5'-TTT GGT CCT TGT CTT ATG TCC AGA ATG C

PROBE
SK 19 5'-ATC CTG GGA TTA AAT AAA ATA GTA AGA
ATG TAT AGC CCT AC

FIG.7

1

POLYMERASE CHAIN REACTION ASSAYS FOR MONITORING ANTIVIRAL THERAPY AND MAKING THERAPEUTIC DECISIONS IN THE TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME

This application is a divisional application of U.S. application Ser. No. 07/883,327, filed May 14, 1992, now abandoned which is incorporated herein by reference in its entirety.

This invention was made with Government support under contracts AI27762-04 and AI27766-07 awarded by the National Institutes of Health. The Government has certain rights in this invention.

1. INTRODUCTION

The present invention relates to methods of monitoring, via polymerase chain reaction, the clinical progression of human immunodeficiency virus infection and its response to antiretroviral therapy. According to the invention, polymerase chain reaction assays may be used to predict immunological decline and to identify, at an early stage, patients whose infection has become resistant to a particular antiretroviral drug regimen.

2. BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) isolated from patients treated with zidovudine (AZT) may demonstrate markedly reduced in vitro susceptibility to AZT (Larder et al., 1989, Science 243:1731–1734; Ronke et al., 1989, AIDS 3:411–415, Land et al., 1990, J. Infect. Dis. 161:326–329; Boucher et al., 1990, Lancet 336:585–590; Japour et al., 1991, Proc. Natl Acad. Sci. 88:3092–96; Tudor-Williams et al., 1992, Lancet 339:15–19). This reduced susceptibility has been related to the duration of therapy with AZT and the severity of HIV disease at the time AZT therapy is begun (Richman et al., 1990, J. AIDS 3:743–756). Nucleotide sequence analysis of AZT-resistant HIV strains has revealed a number of mutations in the reverse transcriptase (RT) gene associated with decreased AZT susceptibility (Larder et al., 1989, Science 246:1155–1158; Larder et al., 1991, AIDS 5:137–144, Kellam et al., 1992, Proc. Natl. Acad.Sci. USA 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559; Richman et al., 1991, J. Infect. Dis. 164:1075–1081). Molecular cloning experiments have confirmed that these mutations in the RT gene confer AZT resistance (Larder et al., 1989, Science 246:1155–1158; Larder et al., 1991, AIDS 5:137–144; Kellam et al., 1992, Proc. Natl. Acad.Sci. USA 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559). Of these mutations the one at codon 215 resulting in a single amino acid substitution (Thr→Tyr or Phe) has been shown to be the most common mutation and to have the greatest impact on in vitro susceptibility to AZT (Larder et al., 1991, AIDS 5:137–144; Richman et al., 1991, J. Infect. Dis. 164:1075–1081; Boucher et al., 1992, J. Inf. Dis. 165:105–110).

Several studies have addressed the relationship between in vitro AZT resistance, mutations in the RT gene and clinical disease. Richman and coworkers studied 32 patients with different stages of HIV disease and demonstrated that the development of in vitro AZT resistance was related to the duration of therapy with AZT and to the severity of disease at the time AZT was begun (Richman et al., 1990, J.AIDS 3:743–746). Boucher and coworkers studied HIV P24-antigenemic patients treated with AZT for 2 years. They observed that at 6 months, seven patients with a mutation at

2

codon 215 had a weak, non-statistically significant trend toward lower CD4 counts compared to nine patients who were wild type at codon 215 (Boucher et al., 1990, Lancet 336:585–590). After 2 years nearly all patents had the mutation. Tudor-Williams and coworkers studied HIV isolates from 19 symptomatic children treated with AZT for 9–39 months and showed that in vitro AZT resistance was associated with poor clinical outcome (Tudor-Williams et al., 1992, Lancet 339:15–19). However, adult studies have not shown a precise correlation between the development of in vitro resistance and progression of HIV disease.

3. SUMMARY OF THE INVENTION

The present invention relates to methods of monitoring, via polymerase chain reaction (PCR), the clinical progression of human immunodeficiency virus (HIV) infection and its response to antiviral therapy. It is based, in part, on the discovery that plasma HIV RNA copy number, as measured using PCR, may be used as a sensitive marker of the circulating HIV viral load to assess the therapeutic effect of antiretroviral compounds. In working examples described herein, an increase in plasma HIV RNA copy number was found to correlate with disease progression, and successful antiretroviral therapy was found to correlate with a decline in plasma HIV RNA copy number.

The invention is also based, in part, on the discovery that genetic changes in HIV which confer resistance to antiretroviral therapy may be rapidly determined directly from patient peripheral blood mononuclear cells (PBMC) and/or plasma HIV RNA using a "nested" PCR procedure. In working examples disclosed herein, a mutation at codon 215 of HIV reverse transcriptase (RT) was found to occur in AZT-treated patients which correlated with refractoriness to AZT treatment. The mutation was found in plasma HIV RNA one to eight months before it was detectable in PBMC. The development of the codon 215 mutation in HIV RT was found to be a harbinger of immunological decline, which occurred between six and twelve months after the mutation was detectable in plasma HIV RNA.

In particular embodiments of the invention, PCR assay may be used to monitor the clinical progression of HIV infection in patients receiving antiretroviral therapy. An increase in plasma HIV copy number detected by such an assay would correlate with refractoriness to treatment. If a patient being treated with an antiretroviral therapeutic agent exhibits an increase in plasma HIV RNA copy number, a physician should consider altering the patients treatment regimen. It should be noted that the present invention offers the advantage of being more sensitive in measuring HIV virus than standard methods which measure plasma p24 antigen or infectious virus detectable by culture techniques.

In further embodiments of the invention, PCR assay may be used to detect mutations at codon 215 of HIV RT which correlate with resistance to antiretroviral therapy and which precede immunologic decline by 6–12 months. Once mutation at codon 215 has been detected in a patient undergoing antiretroviral therapy, an alteration in the therapeutic regimen must be considered. The speed at which a modified regimen should be instituted may depend on whether the mutation is present in plasma HIV RNA or PBMC. If the mutation is present in PBMC, a rapid alteration in therapy may be warranted.

In patients suffering from HIV infection, opportunistic infections arising as a result of a compromised immune system can be rapidly fatal. It is therefore extremely important to strive to avoid deterioration of the immune system in

these patients. Because the present invention enables the early prediction of immunological decline, it allows alteration of a patient's therapeutic regimen so as to avoid opportunistic infections, and therefore may be used to promote survival and improve the quality of life of HIV-infected patients.

4. DESCRIPTION OF THE FIGURES

FIG. 1. Human immunodeficiency virus RNA copy number in 200 μl of plasma from 72 subjects as determined by cDNA gene amplification. Of 39 patients who were not currently receiving antiretroviral therapy, 20 had a CD4 count <200/mm^3 (HIV copy number 1,369±707) and 19 had a CD4 count >200/mm^3 (HIV copy number 44±10). Of 33 subjects who were currently on AZT, 14 had a CD4 count <200/mm^3 (HIV copy number 295±5) and 19 had a CD4 count >200/mm^3 (HIV copy number 16±5). Mean copy number (open circles) of subjects not on therapy was 690±360 as compared to 134±219 for patients currently on AZT ($P<0.05$, independent sample t test).

FIG. 2. Human immunodeficiency virus RNA copy number in plasma from 27 subjects before (pre) and 1 mo after (post) dideoxynucleoside therapy. (o) AZT; (●) AZT+ddI; and (▲) ddI alone. Mean copy number decreased from 540±175 to 77±35 after therapy ($P<0.05$ paired t test).

FIG. 3. Human immunodeficiency virus RNA copy number in plasma from 9 subjects with two samples obtained before initiation of therapy (pre 1 and pre 2) and two samples obtained 1 and 2 mo after commencing therapy (post 1 and post 2). (▲) ddI alone; (●) ddI+AZT.

FIGS. 4A. and 4B. Serial CD4 counts in PBMC (cells/μl) of 17 patients in which HIV reverse transcriptase carried a mutation at codon 215 (4A) and of 21 patients in which HIV reverse transcriptase was wild type at codon 215 (bottom).

FIGS. 5A-5C. CD4 cell counts in PBMC from serial time points in 37 patients. o=wild type sequence in serum specimen, ●=mutant sequence in serum, ↑=wild type sequence in PBMC, ↓=mutant sequence in PBMC; FIGS. $5A_1$ to $5A_{16}$ 16 patients mutant at codon 215 in both serum HIV RNA and PBMC (proviral DNA). FIGS. $5B_1$ to $5B_{10}$ 10 patients mutant at codon 215 in serum HIV RNA but wild type in their PBMC. FIG. 5C: 11 patients whom remained wild type at codon 215 in their serum HIV RNA and PBMC.

FIG. 6. Relationship of PBMC to serum genotypes in the 38 patients at study endpoint.

FIG. 7. Nucleotide sequences of SK38, SK39, and SK19.

5. DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods of monitoring, via PCR, the clinical progression of HIV infection in patients receiving antiretroviral therapy. For purposes of clarity and not by way of limitation, the detailed description of the invention is divided into the following subsections.

(i) PCR assay of plasma HIV RNA;

(ii) PCR assay of peripheral blood mononuclear cells;

(iii) PCR assay for mutation at codon 215 of HIV reverse transcriptase; and

(iv) utility of the invention.

It should be noted that heparin appears to have an inhibitory effect on gene amplification via PCR. It is therefore desireable to avoid using heparin as an anticoagulant of patient blood samples. If heparin has been used in a sample, the sample may be purified of heparin, for example, by collecting virus by ultracentrifugation.

5.1 PCR Assay of Plasma HIV RNA

According to the invention, it is desireable to avoid degradation of RNA in plasma samples prior to measurement of HIV RNA copy number. Therefore, in preferred embodiments of the invention, guanidinium is added to plasma or serum samples prior to storage at a concentration of about 2.5M and samples are kept frozen at −70° C., with no samples stored for longer than about 3 months. Serum may be used interchangeably with plasma according to the invention.

RNA may be extracted from plasma using standard techniques, such as those set forth in Chomczynski and Sacchi, 1987, Ann. Biochem. 162:156–159. For example, 200 μl of clarified plasma to which 200 μl of 5M guanidinium thiocyanate had previously been added may be extracted with phenol/chloroform and precipitated with isopropanol. The resulting pellet may then be washed in 75 percent ethanol, dried, and brought up into solution in diethylpyrocarbonate-treated glass distilled water.

From plasma RNA, HIV RNA may be transcribed to cDNA using a suitable reverse transcriptase (for example, Moloney murine leukemia virus reverse transcriptase) using standard techiques, such as for example, those set forth in Kawasaki, 1990, in "PCR Protocols: A Guide to Methods and Applications," Innis et al., eds., Academic Press, Berkeley, Calif. pp. 21–27. Any suitable primer for amplification of HIV genomic RNA sequences may be used, including, but not limited to, the oligomers SK38, SK39, and SK19 (FIG. 7) described in Kellog et al., 1990, in "PCR Protocols: A Guide To Methods and Applications," Innis et al., eds., Academic Press, Berkeley, Calif. pp. 337–347. In a preferred embodiment of the invention, HIV cDNA may be amplified as follows: to a 100 μl reaction mixture, cDNA prepared as described supra may be added, together with 50 pmol of primers SK38 and SK39, 10 mM of each dNTP, 10 mM Tris (pH 8.3), 2.5 mM $MgCl_2$, 50 mM KCl, and 2.5 U of recombiTaq DNA polymerase (Perkin-Elmer Cetus, Norwalk, Conn.). The mixture may then be overlaid with 50 μl of mineral oil, and tubes containing the reaction may be placed in a DNA thermal cycler (e.g. Perkin-Elmer Cetus) for about 30 cycles of amplification with the following program: 95° C./30 seconds, 55° C./30 seconds, and 72° C./60 seconds for denaturation, annealing, and extension, respectively. Negative and positive controls which include both high and low copy number HIV RNA and DNA may be added at each step.

It is important that the number of cycles not exceed 35, and preferably, only about 30 cycles of amplification are used in the PCR. Using a greater number of cycles may detract from the sensivity of the assay.

The copy number of HIV RNA may then be measured by methods known to the skilled artisan. For example, the number of copies of HIV RNA in a patient sample may be quantiated by hybridizing the product of the above PCR with a detectably labeled probe that is complementary to HIV sequence. The amount of signal generated by probe hybridized to PCR product may then be compared to the amount of signal generated by probe hybridized to a known copy number of HIV. Probe may be detectably labeled by an enzyme, a radioisotope, a fluorescent compound, a chromogenic compound, or any other detectably labeled compound.

In a preferred, nonlimiting embodiment of the invention, at least one of the PCR primers may be biotinylated, probe may be labeled with horseradish peroxidase (HRP), and copy number may be evaluated by an enzyme-linked affinity

assay as follows. 96-well microplates (Maxisorp; Nunc, Naperville, Ill.) may be coated with 100 μl of a 0.1 mg/ml solution of avidin (Sigma Chemical Co., St. Louis, Mo.) in 50 mM Na_2CO_3 (pH 9.6) overnight at room temperature. Wells may then be washed twice with PBS, and then filled with 300 μl of a blocking solution containing 5xDenhardt's solution, 1% gelatin (Sigma), 250 μl/ml sheared herring sperm DNA (Promega Biotec, Madison, Wis.) at least overninght at 4° C. Immediately before use, the blocking solution may be aspirated from each well and 5 μl of PCR product prepared as described supra (using at least one biotinylated primer) may be added to each well together with 65 μl of a hybridization solution containing 5xsaline sodium phosphate EDTA, 5xDenhardt's solution; and 1 pmol of HRP-labeled SK19 HIV gag-specific probe. Because HIV primer was biotinylated, HIV amplified sequences should selectively adhere to the avidin-coated wells, so that a capture and hybridization reaction may be carried out for 1 hour at 42° C. Each well may then be washed about 20 times with PBS containing 0.05% Tween-20, for example, using a Biomek™ 1000 Automated Workstation (Beckman Instruments, Inc., Palo Alto, Calif.). The HRP substrate O-phenylenediamine (Sigma) may then be prepared at 0.6 mg/ml in 0.1 M citrate buffer (pH 5.5) containing 0.03% hydrogen peroxide, and 150 μl of this solution may be added to each well. After about 10 minutes the reaction may be stopped with 1N H_2SO_4 and the optical density of each well measured at 490 nm, for example by the Biomek 1000. A lower level of positivity had been defined as an absorbance of 0.135. This cutoff value was calculated from the mean absorbance obtained from a group of seronegative samples plus three standard deviations. Copy number from subject samples may be determined from the absorbances obtained from a dilution series of an RNA gag gene construct of known copy number (Holodniy et al., 1991, J. Infect. Dis. 163:862–866).

In an alternate preferred, specific embodiment, RNA collected from plasma may be reverse-transcribed by using 500 ng of primer A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1) and 5 units of MuLV RT (Bethesda Research Labs) in 10 μl of amplification buffer (25 mM kCL, 50 mM Tris HCl pH 8.3, 0.1 mg/ml bovine serum albumin, 1.45 mM each of dATP, dGTP, dCTP and dTTP, 1.5 mM $MgCl_2$, and 2.5 U of RNasin (Promega)) for 10 min. at room temperature, then 30 minutes at 42° C. followed by heat inactivation at 95° C. for 5 min. This cDNA may then be amplified by PCR using 250 ng of primer NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2) in a reaction mixture (100 μl) containing the same buffer as above with 0.25 mM of each dNTP and 2.5 U of Amplitaq DNA polymerase, using about 30 cycles of 94° C. for 1 min., 45° C. for 1 min, and 72° C. for 2 min, to generate a 768 bp region of the HIV pol gene.

5.2 PCR Assay of Peripheral Blood Mononuclear Cells

Peripheral blood mononuclear cells (PBMCs) may be used fresh or following cryopreservation (e.g. at −190° C.). DNA may be prepared from PBMCs using standard techniques for use in detection of HIV proviral DNA. Any suitable HIV primer oligonucleotide(s) may be used in PCR to detect HIV provirus.

In a preferred, nonlimiting embodiment of the invention, cryopreserved (−190° C.) PBMC may be treated with a lysis buffer (for example, 0.45 percent Tween-20, 10 mM Tris HCl pH 8.0, 2.5 mM $MgCl_2$, 50 mM KCl, and 0.1 mg/ml proteinase K) for about two hours at 56° C. and then heat inactivated at 95° C. for 10 minutes. Approximately 1 μg of DNA (20 μl of the PBMC lysate) may be used in the initial PCR amplification with primers A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1) and NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2) with reaction conditions as set forth in Larder et al., 1991, AIDS 5:137–144 to generate a 768 bp region of the HIV pol gene.

5.3 PCR Assay for Mutation at Codon 215 of HIV Reverse Transcriptase

To analyse the changes in codon 215 of the HIV pol gene, a "double" or "nested" PCR procedure was performed using the primers, reagents, and reaction conditions described by Larder et al., 1991, AIDS 5:137–144. Five μl of the 768 bp product generated by PCR with primers A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1) and NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2) and either plasma HIV RNA or PBMC DNA may be used in a second series of nested PCR amplifications using primers that detect wild type sequence or sequence mutated at codon 215. In preferred, non-limiting embodiments of the invention, the following primers may be used: to detect wild-type sequence primers B (5'-GGATGGAAAGGATCACC-3') (SEQ ID NO:3) and 3 W (3'-TGGTGTGGTCTGTTTTTTGTA-5') (SEQ ID NO:4) and to detect mutants at codon 215, primers B (supra) and 3M (3'-AAGTGTGGTCTGTTTTTTGTA-5') (SEQ ID NO:5). PCR may then be performed as follows. About 1 μl of template may be used per PCR reaction in 100 μl containing 25 mM KCl, 50 mM Tris HCl pH 8.3, 0.1 mg/ml bovine serum albumin (BSA), 0.2 mM each of dATP, dGTP, dCTP and dTTP, 0.25 μl of each oligonucleotide primer, and 1.5 mM $MgCl_2$. Reaction mixtures may be heated at 100° C. for two minutes prior to addition of Taq DNA polymerase (2.5 U, Perkin-Elmer Cetus, Conn.), overlaid with 100 μl of light mineral oil, and subjected to 30 cycles consisting of a denaturation step (1 minute, 94° C.), primer annealing (30 seconds, 45° C.) and DNA synthesis (30 seconds, 72° C.) using, for example, a Perkin Elmer Cetus DNA thermal cycler. Ten μl of PCR product from each set of "nested" PCR reactions may then be analyzed to determine the presence and intensity of the products. For example, PCR reactions may be analyzed on a 3.0 percent agarose gel with ethidium bromide staining; a portion of a patient sample subjected to "nested" PCR using primers B and 3 W may be run in a lane next to another portion of the same patient sample subjected to "nested" PCR using primers B and 3M. A 210 bp PCR product would be expected; if the patient sample contained HIV RT having the codon 215 mutation, the lane carrying primer B/3M PCR product should exhibit a band that is more intense than any corresponding band in the primer B/3W lane. If the patient sample contained only wild type HIV RT, the band in the primer B/3W lane should be more intense than any corresponding band in the primer B/3M lane. Alternatively, if the patient sample contained a mixture of wild type and mutant HIV RT, bands of similar intensities should be in both lanes.

5.4 Utility of the Invention

The present invention relates to methods of monitoring, via PCR, the clinical progression of HIV infection in patients receiving antiretroviral therapy. Techniques described in Sections 5.1 through 5.3 supra, may be used as set forth below.

In one particular embodiment, the present invention provides for a method of evaluating the effectiveness of anti-

retroviral therapy of a patient comprising (i)collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent; (ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and (iii) testing for the presence of HIV sequence in the product of the PCR; in which the absence of detectable HIV sequence correlates positively with the conclusion that the antiretroviral agent is therapeutically effective and the presence of detectable HIV sequence correlates positively with the conclusion that the antiretroviral agent is therapeutically ineffective. In further, related, embodiments, the presence of detectable HIV sequence correlates positively with an absolute CD4 count of less than 200 cells/mm^3, and the absence of detectable HIV sequence correlates positively with a CD4 count greater than 200 cells/mm^3. The phrase "correlates positively," as used herein, indicates that a particular result renders a particular conclusion more likely than other conclusions.

In another particular embodiment, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent; (ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and (iii) measuring the HIV RNA copy number using the product of the PCR, in which an HIV RNA copy number greater than about 500 correlates positively with the conclusion that the antiretroviral agent is therapeutically ineffective, and an HIV RNA copy number less than about 200 correlates positively with the conclusion that the antiretroviral agent is therapeutically effective.

In a further embodiment, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting one pre-treatment plasma sample from an HIV-infected patient who is about to be treated with an antiretroviral agent; (ii) collecting a post-treatment plasma sample from the HIV-infected patient after the patient has been treated with the antiretroviral agent; (iii) amplifying the HIV-encoding nucleic acid in the pre-treatment and post-treatment plasma samples using HIV primers in about 30 cycles of PCR; (iv) measuring the HIV RNA copy number using the products of the PCRs of step (iii); and (v) comparing the HIV RNA copy number in pre-treatment and post-treatment plasma samples, in which a ratio of HIV RNA copy number in pre-treatment and post-treatment plasma samples of greater than about 4 to 1 correlates positively with the conclusion that the antiretroviral agent is therapeutically effective.

In additional embodiments of the invention, PCR assay may be used to detect mutations at codon 215 of HIV RT which correlate with resistance to antiretroviral therapy and which precede immunologic decline by 6–12 months. Accordingly, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent; and (ii) determining (for example, using "nested" PCR) whether the plasma sample comprises nucleic acid encoding HIV RT having a mutation at codon 215, in which the presence of the mutation correlates positively with immunologic decline of the patient within a six to twelve month period. Under such circumstances, the HIV virus infecting the patient has become, via the mutation, resistant to the antiretroviral agent. It therefore maybe desirable after detecting the mutation, to either increase the dosage of antiretroviral agent, change to another antiretroviral agent, or add one or more additional antiretroviral agents to the patient's therapeutic regimen. For example, if the patient was being treated with zidovudine (AZT) when the mutation arose, the patient's therapeutic regimen may desirably be altered, within about a six to twelve month period of the mutation's occurrence, by either (i) changing to a different antiretroviral agent, such as dideoxyinosine (ddI) and stopping AZT treatment; or (ii) increasing the dosage of AZT; or (iii) adding another antiretroviral agent, such as ddI, to the patient's therapeutic regimen. The effectiveness of the modification in therapy may be evaluated, as set forth above, by monitoring the HIV RNA copy number. A decrease in HIV RNA copy number correlates positively with the effectiveness of a treatment regimen.

Because the mutation at the 215 codon appears first in plasma HIV RNA and later in PBMC proviral DNA, once the mutation is detected in proviral DNA, the treatment regimen is desirably modified with haste in order to avoid immune decline. Accordingly, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting PBMC from an HIV-infected patient who is being treated with an antiretroviral agent; and (ii) determining whether the PBMC comprise proviral HIV DNA which comprises a mutation at codon 215, in which the presence of the mutation correlates positively with immunologic decline of the patient within a 4–11 month period (because, as discussed in Section 7, infra, a mutation in serum HIV RNA was found to precede the mutation in proviral DNA by 1–8 months). Once the mutation is detected in proviral DNA, immune decline becomes even more imminent, and alteration of the patient's therapeutic regimen is desirable.

When immune decline is heralded by the increase in HIV RNA copy number and/or the presence of the mutation at codon 215, in addition to altering the patient's antiretroviral therapy, it may also be desirable to treat the patient prophylactically for opportunistic infections, using antifungal, antibiotic, and/or antiparasitic medications.

Antiretroviral agent, as used herein, includes any known antiretroviral agent including, but not limited to, dideoxynucleosides. In preferred embodiments of the invention the antiretrovital agent is AZT. Resistance to certain antiretroviral agents, including AZT, is associated with a mutation at codon 215. Resistance to other antiretroviral agents, such as ddI, is associated with a mutation at codon 74 (74) The present invention provides for analogous techniques in which the effectiveness of antiretroviral therapy is monitored by determining whether plasma HIV RNA or PBMC contain a mutation at codon 74 of HIV RT, in which a mutation at that locus may augur immunological decline and may warrant a modification of antiretroviral therapy.

One preferred, non-limiting, specific embodiment of the invention is as follows: A method of evaluating the effectiveness of AZT therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with AZT, (ii) amplifying the HIV-encoding RNA in the plasma sample by converting the RNA to cDNA and amplifying HIV sequences using HIV primers in about 30 cycles of PCR; and (iii) testing for the presence of HIV sequence in the product of the PCR, in which the absence of detectable HIV sequence correlates positively with the conclusion that AZT is therapeutically effective and the presence of detectable HIV sequence correlates positively with the conclusion that AZT is therapeutically ineffective. In most preferred embodiments, the HIV primers used comprise NE1 (supra), SK38 and/or SK39 (supra), and/or the presence of HIV sequence is detected using an enzyme-

linked assay (e.g., a horseradish peroxidase based assay). Similar embodiments in which the HIV copy number is measured are also provided for.

Another preferred, non-limiting, specific embodiment of the invention is as follows: A method of evaluating the effectiveness of AZT therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with AZT; (ii) amplifying the HIV-encoding RNA in the plasma sample by converting the RNA to cDNA and amplifying HIV sequences using HIV primers that result in a PCR product that comprises that portion of the RT gene that contains the 215 codon (e.g. primer NE1, supra); (iii) performing "nested" PCR using primers that result in PCR products that reflect the presence of wild type (e.g. primers B and 3W, supra) or 215 codon mutant (e.g. primers B and 3M, supra); and (iv) determining, via the products of "nested" PCR, the presence or absence of a mutation at codon 215 of the HIV RT, in which the presence of the mutation correlates positively with immunologic decline of the patient within a six to twelve month period. An analogous method may be used in which the patient sample is PBMC, and the presence of a mutation is proviral DNA is determined.

6. EXAMPLE: REDUCTION IN PLASMA HUMAN IMMUNODEFICIENCY VIRUS RIBONUCLEIC ACID AFTER DIDEOXYNUCLEOSIDE THERAPY AS DETERMINED BY THE POLYMERASE CHAIN REACTION

6.1 Materials and Methods

6.1.1 Patients

After informed consent was obtained, whole blood samples were collected by venipuncture in the presence of acid-citrate-dextrose as an anticoagulant. A single plasma sample was collected from 39 HIV antibody-positive subjects who were not receiving antiretroviral therapy at the time of collection and from 33 HIV antibody-positive subjects who were currently on and had received AZT for a minimum of 3 mo.

Two plasma samples were collected from an additional 27 subjects before and 1 month after initiation of dideoxynucleoside therapy. 18 of these subjects received 500 mg/d of AZT orally. Seven subjects received a combination of zidovudine (150–600 mg/d) and 2',3'-dideoxyinosine (ddI) (134–500 mg/d). Two patients received 500 mg/d of ddI alone (see Table 1 for individual subject characteristics). Finally, nine of these subjects had two plasma samples taken 1–3 wk. before initiating antiretroviral therapy and two plasma samples taken 1 and 2 mo. after commencing therapy. Plasma was separated within 4 h. by centrifugation at 500 g for 10 min. A second centrifugation was performed on the plasma at 500 g for 30 min. to remove any cellular material. 200 μl of plasma was then mixed with 200 μl of a solution containing 5 M guanidinium thiocyanate, vortexed briefly, and stored at −70° C. until further use. All samples were assayed within 3 mo. of collection. To decrease variance, all specimens to be compared from the same subject were run in the same assay.

6.1.2 Extraction of RNA from Plasma

RNA was extracted from plasma by the method described in Chomczynski et al., 1987, Ann. Biochem. 162:156–159. Briefly, 200 μl of clarified plasma to which 200 μl of 5 M guanidinium thiocyanate had previously been added was extracted with phenol/chloroform and precipitated with isopropanol. The resulting pellet was then washed in 75% ethanol, dried, and brought up in diethylpyrocarbonate treated, glass distilled water.

6.1.3 Reverse Transcription and Amplification of cDNA

HIV RNA was transcribed to cDNA using Moloney murine leukemia virus reverse transcriptase (Bethesda Research Laboratories, Gaithersburg, Md.) by the method described in Kawasaki, 1990, "In PCR Protocols: A Guide to Methods and Applications" pp. 21–27, M. A. Innis, D. H. Gelfand, J. J. Sninsky, and T. J. White, eds. Academic Press, Berkeley, Calif. Oligomers used for amplification included SK38, SK39, and SK19 (Kellog et al., 1990, "In PCR Protocols: A Guide to Methods and Applications," pp. 337–348, M. A. Innis, D. H. Gelfand, J. J. Sninsky, and T. J. White, eds. Academic Press, Berkeley, Calif.). Biotinylation of SK38 and horseradish peroxidase (HRP) labeling of probe SK19 were prepared as described in Levenson et al., 1990, "In PCR Protocols: A Guide to Methods and Applications," pp. 99–112 M. S. Innis, D. H. Gelfand, J. J. Sninsky, and T. J. White, eds. Academic Press, Berkeley, Calif. Amplification of HIV cDNA was carried out as follows: to a 100-μl reaction mixture was added the cDNA, 50 pmol of primers SK38 and SDK39, 10 mM of each dNTP, 10 mM Tris (pH 8.3), 2.5 mM $MgCl_2$, 50 mM KCl, and 2.5 U of recombiTaq DNA polymerase (Perkin-Elmer Cetus, Norwalk, Conn.). The mixture was then overlaid with 50 μl of mineral oil. Tubes were placed in a DNA thermal cycler (Perkin-Elmer Cetus) for 30 cycles of amplification with the following program: 95° C./30 s, 55° C./30s, and 72° C./60 s for denaturation, annealing, and extension, respectively. Negative and positive controls which included both high and low copy number HIV RNA and DNA were added at each step.

6.1.4 Enzyme-linked Affinity Assay

To detect and quantitate PCR product, 96-well microplates (Maxisorp; Nunc, Naperville, Ill.) were coated with 100 μl of a 0.1 mg/ml solution of avidin (Sigma Chemical Co., St. Louis, Mo.) in 50 mM Na_2CO_3 (pH 9.6) overnight at room temperature. Wells were then washed twice with PBS. Wells were then filled with 300 μl of a blocking solution containing 5xDenhardt's solution, 1% gelatin (Sigma), 250 μl/ml sheared herring sperm DNA (Promega Biotec, Madison, Wis.) at least overnight at 4° C. Immediately before use, the blocking solution was aspirated from each well and 5 μl PCR product and 65 μl of a hybridization solution, containing 5xsaline sodium phosphate EDTA, 5xDenhardt's solution, and 1 pmol of HRP-labeled SK19 HIV gag specific probe was added to each well. A capture and hybridization reaction was then carried out in the well for 1 h. at 42° C. The 96 well microplate was then placed in a Biomek™ 100 Automated Workstation (Beckman Instruments, Inc., Palo Alto, Calif.) where wells were washed 20 times with BPS containing 0.05% Tween-20. The HRP substrate O-phenylenediamine (Sigma) was prepared at 0.6 mg/ml in 0.1 M citrate buffer (pH 5.5) containing 0.03% hydrogen peroxide. 150 μl of this substrate solution was added to each well. After 10 min. the reaction was stopped with 1 N H_2SO_4 and the optical density of each well measured at 490 nm by the Biomek 1000. A lower level of positivity had been defined as an absorbance of 0.135. This cutoff value was calculated from the mean absorbance obtained from a group of seronegative samples plus three standard deviations. Copy number from subject samples were determined from the absorbances obtained from a dilution series of an RNA gag gene construct of known copy number described in Holodniy et al., 1991, J. Infect. Dis. 163:862–866. The lower level of sensitivity in this assay was 40 copies of HIV gag gene RNA.

6.1.5 Plasma HIV Culture and P24 Antigen Assay

Quantitative HIV plasma microculture was performed according to the method described in Ho et al., 1989, N. Engl. J. Med. 321:1621–1625. P24 antigen was detected by an antigen capture assay by a method provided by the supplier (Abbott Laboratories, North Chicago, Ill.).

6.1.6 Statistical Analysis

Sample optical density was converted to copy number and analyses performed on samples expressed as RNA copy number/200 μl of plasma. A t test of independent samples was used in analysis of subject who did not receive antiretroviral therapy compared to subjects who were receiving AZT. A t test of paired samples was used to analyze paired plasma data and CD4 counts from subjects pre- and post-therapy. All t tests were two tailed. A Fisher's exact test or chi square test were used for analysis of proportion where appropriate. Statistical significance was defined as $P<0.05$.

6.2 Results

72 subjects were evaluated in a cross-sectional study of HIV disease to determine plasma HIV RNA copy number by PCR. The results are presented in FIG. 1. 39 subjects who were not currently receiving antiretroviral therapy and 33 subjects who were receiving AZT were evaluated. Untreated subjects were more likely to have a positive signal than treated subjects (32 of 39 vs. 16 of 33, respectively, P 0.008, chi square). In the 39 subjects who were not currently receiving therapy, the mean plasma HIV RNA copy number was 690±360 (mean±SEM) per 200 μl of plasma, while the 33 subjects who had been receiving AZT therapy had a mean copy number of 134±219 ($P<0.05$). Mean CD4 count for each group was 316±45 and 300±37, respectively (P=NS).

Subgroups were then analyzed with respect to CD4 count. Among those with <200 CD4 cells, untreated subjects were more likely to have positive signal than treated subjects (18 of 19 vs. 9 of 14, $P<0.04$, Fisher's exact test). Among those with >200 CD4 cells, 14 of 20 untreated subjects vs. 7 of 19 treated subjects had a detectable signal (P=NS, Fisher's exact test). Untreated subjects with CD4 count <200/mm^3 had a mean RNA copy number of 1,369±707 and mean CD4 count of 73±17; untreated subjects with CD4>200/mm^3 had a mean RNA copy number of 44±10 and mean CD4 count of 547±45; treated subjects with CD4 counts <200/mm^3 had a mean RNA copy number of 295±5 and mean CD4 count of 115±13; and treated subjects with CD4 counts >200/mm^3 had calculated mean RNA copy number of 16±5 (which is below the level of detection of this assay and would be interpreted as negative) and mean CD4 count of 437±41.

27 additional subjects were then evaluated before and 1 mo after initiation of dideoxynucleoside therapy. Clinical parameters of the subjects are presented in Table 1. PCR results are presented in FIG. 2. Results show that plasma HIV RNA copy number fell from 540±175 to 77±35 after therapy ($P<0.05$, paired t test). Mean CD4 count increased from 399±24 to 442±25 after 4 wk of therapy ($P<0.006$, paired t test).

TABLE 1

Clinical Parameters and PCR Analysis of Plasma HIV RNA from 27 Patients

Patient No.	Antiviral treatment	Pre/post CD4	Pre/post HIV RNA
1*	AZT‡	647/561	106/90
2*	AZT	541/651	1300
3	AZT	840/874	5500
4	AZT	432/462	100/77

TABLE 1-continued

Clinical Parameters and PCR Analysis of Plasma HIV RNA from 27 Patients

Patient No	Antiviral treatment	Pre/post CD4	Pre/post HIV RNA
5*	AZT	379/415	87/57
6*	AZT	428/408	40/42
7	AZT	422/345	94/94
8	AZT	420/402	0/0
9	AZT	432/532	93/65
10	AZT	430/430	105/52
11	AZT	429/404	123/90
12	ddI + AZT§	280/220	526/0
13	AZT	324/320	78/45
14	AZT	330/456	95/95
15	AZT	354/387	301/0
16	ddI + AZT§	309/399	300/0
17	ddI + AZT§	337/398	260/0
18	ddI¶	328/310	966/0
19	ddI + AZT¶	383/491	245/0
20	AZT	404/413	0/0
21	AZT	270/450	958/72
22	ddI + AZT¶	292/344	60/0
23	AZT	330/295	2769/437
24	ddI¶	222/370	3944/0
25	AZT	568/730	2014/925
26	DDI + AZT**	367/473	217/0
27	DDI + AZT**	310/399	4.9/0

*Remote history of AZT use.
†AZT dose 500 mg/d unless otherwise stated.
‡AZT 300 mg/d + ddI 334 mg/d.
§ddI 500 mg/d.
¶AZT 600 mg/d + ddI 500 mg/d.
**AZT 150 mg/d + ddI 134 mg/d.

Finally, 9 of the 27 subjects had two samples taken before initiation of therapy and two samples taken 1 and 2 months after commencing therapy. The results are presented in FIG. 3. When two pretherapy time points were analyzed for constancy of signal, results show that mean copy number for each pretherapy time point was 945±377 and 643±392.

Two subjects had a second pretherapy sample which was negative. When both pretherapy copy number values were compared to postitherapy values, plasma HIV RNA copy number fell from 794±274 to <40 (which is below the lower level of detection in this assay) after 1 and 2 mo of therapy ($P<0.05$, paired t test). Mean CD4 count increased from 314±165 to 378±25 ($P<0.05$, paired t test).

Plasma culture was performed on fresh material obtained from the initial pretreatment sample for 23 of 27 of these patients. Only 7 of 23 were plasma virus positive by culture (from 1 to 100 tissue culture infective does/ml). All 23 of these patients were positive by PCR (>40 copies/200 μl). In addition, a p24 antigen test was performed on all 27 pre-treatment samples. Only 2 of 27 had detectable p24 antigen present (>30 pg/ml).

6.3 Discussion

The results presented here demonstrate that plasma HIV RNA can be detected and quantified by copy number in the majority of patients infected with HIV. In addition, plasma HIV RNA copy number may be used as a marker of circulating HIV viral load to assess treatment effect of antiretroviral compounds including dideoxynucleoside compounds. We initially conducted a survey to determine whether treatment or degree of immunologic impairment, based on CD4 count, affected plasma HIV RNA copy number. Untreated patients as a group had higher copy numbers than treated patients. Untreated patients with <200

CD4 cells/mm^3 had a higher mean copy number than patients with >200 CD4 cells/mm^3. Likewise, treated patients with <200 CD4 cells/mm^3/ had higher copy numbers than patients with >200 CD4 cells/mm^3, indicating that patients with more advanced HIV disease have higher circulating copy numbers than asymptomatic patients, and that the antiretroviral benefit seen in patients with higher CD4 counts may be waning.

To assess the short-term impact of antiretroviral therapy on patients, 27 patients were evaluated before and 1 mo after initiation of AZT, ddI, or combination therapy. As CD4 counts increased after 1 mo of therapy, HIV RNA copy number fell significantly. However, the response of individual subjects was variable. 16 of 27 subjects had a marked decrease in copy number and 11 of 27 did not. Because the majority of subjects received AZT alone, it was not possible to assess any differences between AZT, ddI, or combination regimens.

Finally, nine subjects had two baseline time points taken in the 3 wk before treatment, followed by two monthly samples posttreatment. Pretreatment signal was constant in 7 of 9 subjects, and 2 subjects had discordant samples, i.e., one was positive and one was negative. This could be related to real changes in circulating HIV RNA, or introduced during sample collection, handling, or the assay. However, pretherapy and posttherapy samples were run in the same assay and so were subject to all of the same reaction conditions. When sample positivity was considered in relation to therapy, 16 of 18 pretherapy samples had a positive signal vs. 0 of 18 posttherapy samples ($P<0.001$, chi square) showing suppression of HIV RNA copy number with treatment.

Currently there is no standard method to assess circulating viral load in all HIV-infected patients. Plasma viremia, measured by quantitative microculture, can identify and quantify infectious virus in 50–100% of patients, principally those with advanced stages of HIV disease, low CD4 counts, and p24 antigenemia (Ho et al., 1989, N.Engl. J. Med. 321:1621–1625; Coombs et al., 1989, J. Virol. Methods 26:23–21; Ehrnst et al., 1988, N.Engl.J.Med. 324:961–964). Many patients with >200 CD4 cells/mm^3 do not have detectable infectious plasma viremia. This may be due to an absence of circulating infectious virus, virus which is neutralized by specific antibody, or the insensitivity of culture techniques. The results presented here indicate that the majority of patients with >200 CD4 cells/mm^3 do not have plasma p24 antigen or infectious virus detectable by culture techniques. In the studies described herein, it appears that virus undetectable by culture methods was detectable by PCR methods.

Attempts have been made to assess HIV viral load in patients by molecular techniques, mainly by quantitative PCR of HIV proviral DNA in circulating mononuclear cells or cell-free virion-associated RNA in plasma. Published data suggest that the number of cells infected with HIV increases with advancing disease and that HIV proviral DNA content increases as well. We and others have shown a decrease in HIV proviral DNA with dideoxynucleoside therapy over time (Aoki et al., 1990, AIDS Res. Hum. Retroviruses 6:1331–1339). This was not the case in another published small series (McElrath et al., 1991, J.Clin. Invest. 87:27–30).

We have shown that HIV RNA could be quantified in serum and that copy number increased with disease progression (Holodniy et al., 1991, J Infect.Dis. 163:862–866). Plasma HIV RNA has been shown to be present before and after seroconversion with quantitative decreases occurring after seroconversion (Hewlett et al., 1988, J.Clin. Immunoassay 11:161–164). The recent report by Daar et al. (Daar et al., 1991, N.Engl. J.Med. 324:961–964), showed a decrease in both plasma viremia and proviral DNA from PBMC, coinciding with seroconversion after acute infection. In one report, plasma HIV RNA levels fell with passive immunoglobulin therapy, suggesting a therapy-based response in circulating HIV RNA load (Karpas et al., 1990, Proc. Natl. Acad.Sci. USA 87:7613–7617). Ottman and colleagues have been successful in detecting HIV RNA in plasma from 95% of patients evaluated (Ottman et al., 1991, J. Virol. Methods 31:273–284). They also studied a group of patients who were receiving AZT to determine whether there was any therapeutic impact on HIV RNA signal. 24 of 25 patients who were receiving AZT had detectable signal. However, methodological differences in that study vs. the present study may have contributed to the differences noted between them. First, Ottman et al. used an ultracentrifugation step to sediment virus, enhancing virion-associated RNA recovery. Second, 40 cycles of amplification after reverse transcription were performed, which would certainly increase the sensitivity of such an assay to successfully detect HIV RNA in virtually all patients. Although sensitivity is increased with increased cycle number, thus detecting signal in virtually all patients, the ability to show the quantitative changes demonstrated here with 30 cycles of amplification is lost.

We have previously shown in serum that quantitative serum cultures were negative in the majority of patients with >200 CD4 cells/mm^3 (Holodniy et al. 1991, J. Infect.Dis. 163:862–866). In the current study, 23 plasma samples were evaluated by culture and PCR. All had detectable plasma HIV RNA by PCR< but only seven were plasma HIV-culture positive. Other published experience comparing plasma HIV culture and PCR of HIV RNA from plasma is lacking. Ottman et al. tested only two patients, both of whom were positive in both assays. Coyle et al. reported that 14 of 20 patients had positive plasma cultures and 12 of 20 patients had detectable HIV RNA in plasma, but no information was given regarding concordance or discordance of samples (Coyle et al., 1990, Clin. Res. 38:778a (Abstr.)).

The type of plasma sample and method of processing and storage were found to be very important. The type of anticoagulant used for sample collection can affect detection of plasma RNA. We have previously shown that plasma collected in the present of heparin does not allow detection of signal because of an inhibitory effect of heparin on gene amplification (Holodniy et al., 1991, J.Clin. Microbiol. 29:676–679). Although Coyle et al. (1990, Clin. Res. 38:778a (Abstr.)) found detectable signal from plasma collected in the presence of heparin, an ultracentrifugation step preceding RNA analysis lead to removal of most of the heparin from the enzyme-mediated assay system. However, no comparison experiments among anticoagulants were performed to demonstrate any attenuation of signal obtained in the presence of heparin.

Because of our concern for RNA degradation during specimen storage and freeze thawing, we decided to store fresh plasma at −70° C. in the presence of guanidinium and process samples within 3 mo of collection. Samples were stored in guanidinium for RNAase inhibition. Preliminary data from our laboratory would suggest that plasma HIV RNA signal decays with time in the absence of this RNA stabilizer.

In summary, we have shown that plasma HIV RNA copy number can be quantitated by PCR and does decrease with

dideoxynucleoside therapy. The nonisotopic, microplate-based format presented here makes it possible to process multiple patient samples with replicates in a single amplification and assay run.

7. EXAMPLE: RELATIONSHIP OF A MUTATION IN THE HIV REVERSE TRANSCRIPTASE GENE TO DECLINE IN CD4 LYMPHOCYTE NUMBERS IN LONG TERM AZT RECIPIENTS

7.1 Materials and Methods

7.1.1 Study Population

Cryopreserved PBMC and serum from 40 participants in AIDS Clinical Trial Group (ACTG) protocols 019 (30 patients) and 016 (10 patients) at Stanford University Medical Center AIDS Clinical Trial Unit were used in this study. Patients at enrollment in these studies were AZT naive, had >200 CD4 cells/μl and had few (016) or no symptoms (019) referable to HIV infection. They were subsequently treated with AZT for 2 to 4 years. The most common dosage was 500 mg per day. Approximately one third of patients received either 1200 mg or 1500 mg per day during the initial part of their therapy, but were changed to 500 mg per day when lower doses were found to be as effective but less toxic than higher doses (Fischl et al., 1990, N. Engl. J. Med. 323:1009–1014; Volberding et al., 1990, N. Engl. J. Med. 322:941–949). All samples were obtained from the patients while they were on the protocols and thus no patient developed an AIDS defining diagnosis.

7.1.2 CD4 Cell Counts

CD4 cell counts were obtained approximately every three months on each patient. All counts were performed at Stanford's ACTG-qualified cytofluorometry lab. Samples were stained with monoclonal antibodies to CD3, CD4, and CD8. The absolute CD4 count was calculated by multiplying the percent CD4 by the total lymphocyte count.

7.1.3 PBMC Preparation

Cryopreserved (−190° C.) PBMC were treated with a lysis buffer (0.45% Tween-20, 10 mM Tris HCl pH 8.0, 2.5 mM $MgCl_2$, 50 mM KCl, and 0.1 mg/ml proteinase K) for 2 hours at 56° C. and then heat inactivated at 95° C. for 10 min. Approximately 1ug of DNA (20 μl of the PBMC lysate) was used in the initial PCR amplification with primers A(5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1) and NE1(5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2) with reaction conditions as described in Larder et al., 1991, AIDS 5:137–144 to generate a 768 bp region of the HIV pol gene.

7.1.4 Serum HIV RNA Preparation

Cryopreserved (−70° C.) serum was thawed and then 350 μl of sera was added to 350 μl of solution D (Chomczynski et al., 1987, Anal. Biochem. 162:156–159) (guanadinium thiocyanate+2-mercaptoethanol) and vortexed. RNA was then extracted with phenol and chloroform and precipitated with ethanol as described in Chomczynski et al., 1987, Anal. Biochem. 162:156–15918. HIV RNA was then reverse transcribed to cDNA by using 500 ng of primer A and 5 units of murine leukemia virus (MuLV) reverse transcriptase (Bethesda Research Labs) in 10 μl of amplification buffer (25 mmol/L KCl, 50 mmol/L Tris HCl Ph 8.3, 0.1 mg/ml bovine serum albumin, 1.45 mmol/L each of dATP, dGTP, dCTP and dTTP, 1.5 mmol/L $MgCl_2$, 2.5 units of RNasin (Promega)) for 10 min at room temperature, then 30 min at 42° C. followed by heat inactivation at 95° C. for 5 min. This cDNA was then amplified by PCR using 250 ng of primer NE1 in a reaction mixture (100 μl) containing the same buffer as above with 0.25 mmol/L of each dNTP and 2.5 units of AmpliTaq DNA polymerase (Perkin-Elmer Cetus). This reaction mixture underwent 30 cycles of 94° C. for 1 min, 45° C. for 1 min and 72° C. for 2 min to generate a 768 bp region of the HIV pol gene.

7.1.5 PCR Analysis of HIV Reverse Transcriptase Gene

To analyze the changes in codon 215 of the HIV pol gene, a "double" PCR procedure was performed using the primers, reagents, and reaction conditions described in Larder et al., 1991, AIDS 5:137–144. Five μl of the 768 bp product generated by PCR with primers A and NE1 was used in a second series of nested PCR amplifications using primer B and 3W to determine if a wild type sequence was present, or B and 3M to determine if a mutant sequence was present (primer sequences as set forth supra and in Larder et al., 1991, AIDS 5:137–144). Samples were run with negative, positive and reaction mixture controls. Ten μl of PCR product from each of the second set of PCR reactions were analyzed on a 3.0% agarose gel with ethidium bromide staining. PCR products were considered to have a mutant or wild type sequence by the method described by Boucher et al. (1990, Lancet 336:585–590; 1992, J. Infect. Dis. 165:105–110) and Larder et al., 1991, AIDS 5:137–144: a sample was considered to contain the wild type sequence at codon 215 if amplification with the primers B and 3W resulted in a 210 bp PCR product of highest intensity; a sample was considered to contain a mutant sequence at codon 215 if amplification with the primers B and 3M resulted in a 210 bp PCR product of highest intensity. The sample was considered to have a mixture of wild type and mutant sequences if amplification occurred with both primers 3M and 3 W resulting in PCR products of similar intensity. If a mixture was detected by PCR then that sample was included in the mutant group in our statistical analysis.

7.1.6 AZT Sensitivity Assay

Patient PBMC were cocultured with mitogen-stimulated PBMC from healthy HIV seronegative donors. Supernatants from these cultures were collected and frozen when the HIV P24 antigen concentration exceeded 10,000 pg/ml. 30–100 $TCID_{50}$ (50% tissue culture infectious dose) of virus stock was used to infect one million donor PBMC pretreated with different concentrations of AZT (0.0 uM, 0.005 uM, 0.05 uM, 0.5 uM, 5.0 uM). After 7 days, P24 antigen was measured in the cell free supernatant from the cultures with and without zidovudine. The concentration of AZT required to inhibit P24 production by 90% (IC_{90}) as compared to the drug free cultures was determined by nonlinear regression analysis (Chou et al., 1984, Adv. Enzyme Regulation 22:27–55). In this assay, the IC_{90}s from AZT-naive patients ranged from 0.002 μM to 0.038 μM AZT.

7.1.7 Statistical Analysis

All comparisons between the patients with mutant and wild type strains were performed using the student's t-test. The calculations on the IC_{90}s determined by the zidovudine sensitivity assay were performed using the $\log_{10}$ transformed IC_{90} (i.e. geometric means were used rather than arithmetic means).

7.2 Results

7.2.1 PCR Analysis of Codon 215 in PBMC

Proviral DNA was detected by nested PCR in the PBMC of 38 of 40 patients after a mean 34 month treatment period. The two patients in whom proviral DNA could not be detected had high CD4 counts at the time their PBMC were analyzed (729 and 676 cells/μl). PCR amplification of the

PBMC from 17 of 38 patients (45%) yielded a 210 bp product with the mutant primer, indicating the presence of a mutation at codon 215 (Thr to Tyr or Phe). The PBMC from 21 of 38 patients (55%) demonstrated amplification product only with the wild type primer (a 210 bp product) indicating the presence of Thr at codon 215.

The mean length of therapy and starting CD4 counts for the two groups were similar (Table 2). However, the 17 patients with a mutation at codon 215 of HIV RT in PBMC proviral DNA had a 50% decrease in their absolute CD4 count between the time they began therapy (378 cells/μl) and the end of the study (189 cells/μl). The 21 patients with a wild type sequence at codon 215 experienced a mean 11% increase in their absolute CD4 count between the time they began therapy (397 cells/μl) and the end of the study (424 cells/μl). The post-treatment CD4 percentages of the two groups of patients were also significantly different (25% in patients with wild-type sequence vs 14% in patients with a mutation in RT at codon 215) (Table 2). The CD4 counts at each time point for each patient are shown in FIGS. 4A and 4B.

TABLE 2

CORRELATION OF PATIENT CD4 COUNT CHANGES WITH PCR ANALYSIS OF CODON 215 OF HIV REVERSE TRANSCRIPTASE IN PBMC

	Wildtype	Mutant	p
Number of patients	21	17	
Months of AZT	33 ± 8	35 ± 7	0.4
Starting CD4 measurements			
Absolute CD4 (cells/μl)	397 ± 124	378 ± 96	>0.5
CD4 %	26 ± 8	25 ± 6	>0.5
CD4 measurements at a time of PCR analysis			
Absolute CD4 (cells/μl)	424 ± 210	189 ± 98	<0.0001
CD4 %	25 ± 9	14 ± 6	0.0001

7.2.2 PCR Analysis of Codon 215 in HIV RNA From Serum

Serial PBMC samples from earlier time points were available on 8/40 patients; however, serial serum samples from earlier time points were available on 37/40 patients. In these 37 patients, 135 serum samples were tested for the presence of a codon 215 mutation. In 87% of these samples (117), reverse transcribed cDNA could be detected by PCR. Fifteen of the 18 sera that were negative by PCR had been previously subjected to multiple freeze-thaws and therefore could be falsely negative. As all patients were AZT-naive, they were assumed to be wild type at codon 215 at the start of AZT therapy.

Twenty-six of the 37 patients developed a mutation in their HIV RNA. This included the 16 who were also mutant in their PBMC at the end of the study period (FIGS. $5A_1$–$5A_{10}$), and ten patients who were wild type in their PBMC but mutant in serum HIV RNA at the end of the study period (FIGS. $5B_1$–$5B_{10}$). The time preceding the occurrence of the 215 mutation in their serum ranged from 2 to 44 months of therapy. Among these 26 patients, the mean CD4 count at the start of therapy was 398±139 cells/μl and their mean CD4 count at the time of first detection of a codon 215 mutation in their serum was 444±206 cells/μl. Nineteen of the 26 patients with a codon 215 mutation in their serum had follow-up CD4 counts at least 12 months after the mutation was first detected. In these 19 patients, there was a mean decrease of 100±116 CD4 cells/μul (25% decline) at six months and a mean decrease of 170±121 CD4 cells/μl (40% decline) at 12 months.

The 11 patients who remained wild type in their serum over the entire 34 month period of zidovudine therapy had an increase of 7±92 CD4 cells/μl (2% increase), (FIG. 5C). The mean CD4 count at the start of therapy for the patients who later developed a mutant in their serum was 398±139 cells/μl and this was not significantly different than the starting CD4 counts for those patients who remained wild type (397±115 cells/μl, p>0.5). The average length of therapy for both groups was 34 months.

7.2.3 Serum Virus Compared to PBMC Provirus

At the final evaluation of the 38 patients after a mean 34 months of zidovudine, 11 patients were wild type in both serum and PBMC, 17 were mutant in both serum and PBMC, and 10 patients had a mutation in their serum but remained wild type in their PBMC FIG. 6. Eight of the 17 patients with a mutation in proviral DNA at the end of the study period had at least one PBMC sample available from an earlier time point. In these eight patients, a mutation in serum HIV RNA preceded the mutation in proviral DNA by 1–8 months. The findings in these 8 patients and in the 10 patients who were wild type in their PBMC but mutant in their serum shows that detection of the serum mutation precedes detection of the mutation in PBMC. In no instance, did a mutation in patient's PBMC precede its appearance in serum.

7.2.4 AZT Sensitivity Results Determined By Cell Culture

In vitro AZT susceptibility testing was performed on 17 of 38 patients using a different aliquot of the same post-treatment PBMC that were used for the PCR analysis. The geometric mean of the IC_{50}s of eight patients with the wild type form at 215 was 0.04 μm AZT (range: 0.02–0.28 μm); the geometric mean IC_{50} of nine patients with a mutation at codon 215 was 0.41 μm AZT (range: 0.03–8.0 μM, p=0.002).

7.3 Discussion

As an increasing number of HIV infected individuals are offered early treatment with AZT, the significance of drug resistant virus has become an important question. In the present study we found a strong correlation between the presence of a mutation at codon 215, which is linked to AZT resistance and an accelerated decline in CD4 cell number. The patients we studied all began taking AZT when their CD4 cell numbers were relatively high and before the onset of AIDS. We observed that the 17 patients with a mutation at codon 215 in proviral DNA in their PBMC experienced a mean 50% decrease in their CD4 count between the time that they began therapy and the time that their cells were analyzed for mutations. The 21 patients who were wild type at codon 215 in their proviral DNA at the end of treatment experienced a mean 11% increase in their CD4 count during the same time period.

Patient cells were only available during the last year of the study. However, by extracting and reverse transcribing HIV RNA from patient's serum specimens we were able to detect codon 215 mutation at earlier time points. The patients in our study with and without a mutation in serum HIV had similar starting CD4 counts (397±115 vs. 398±139, p>0.5) and similar lengths of therapy (34 months in both groups). Yet we found that those patients who develop a mutation in HIV RNA had a subsequent 40% decline in their CD4 cells over the next 12 months. The patients who remained wild type in their serum had a 2% increase in their CD4 cells over 34 months of therapy.

These results show that genetic changes in the virus which confer drug resistance can be rapidly determined directly form patient PBMC and HIV RNA in patients serum using a nested PCR procedure. By using PCR we were able to detect viral nucleic acid in 90% of PBMC samples and 87% of serum samples. Techniques which require culturing HIV from PBMC or serum may select HIV subpopulations with greater tropism for certain cells (Kusumi et al., 1992, J. Virol. 66:875–885; Meyerhans et al., 1989, Cell 58:901–910). This may complicate the analysis of the clinical significance of AZT resistance detected by phenotypic assays.

Earlier clinical studies focused on AZT resistance in patients with initially low CD4 cell counts or who were at high likelihood of disease progression. Furthermore, these studies tested HIV isolates which had been passaged in culture. In contrast, in this study we did not select patients at high likelihood for disease progression but instead we included all patients who remained on AZT for at least 2 years and who had high CD4 counts at the beginning of the study; codon 215 mutations in serum virus occurred early in treatment. The mean CD4 count at the first appearance of the mutation was higher than the CD4 count at the start of therapy (444 vs. 398 cells/μl). This suggests that mutation of the reverse transcriptase gene is not dependent upon low CD4+T cells. On the other hand, we also found that a large percentage of patients remained wild type at codon 215 and phenotypically sensitive to AZT despite almost 3 years of therapy. This may be because our patients were less advanced in their disease or that by using PCR instead of coculture we were able to include patients whose virus might not have grown in culture. These results also suggest that the PBMC may not be the initial source of mutant virus, as evidenced in 18 of our patients where the serum HIV RNA mutation preceded that in PBMC by many months. The source of the mutant HIV detected in serum may be cells in lymphatic, central nervous system or reticuloendothial sites.

The significance of specific mutations in the RT gene with respect to AZT resistance has been defined in patient isolates as well as through molecular cloning experiments (Larder et al., 1989, Science 246:1155–1158; Larder et al., 1991, AIDS 5:137–144; Kellam et al., 1992, 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559). Of the four mutations first reported to be associated with AZT resistance (codons 67, 70, 215, 219), the mutation at codon 215 has been shown to be the most commonly occurring and to have the greatest impact on susceptibility. This impact on AZT susceptibility will vary depending on whether or not additional mutations are present (Larder et al., 1989, Science 246:1155–1158; Larder et al., 1991, AIDS 5:137–144; Kellam et al., 1992, 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559; Richman et al., 1991, J. Infect. Dis. 164:1075–1081; Boucher et al., 1992, J. Infect.Dis. 165:105–110). Recent sequencing studies of clinical isolates suggest that there are additional mutations in the RT gene that may contribute to AZT resistance (Japour et al., 1991, Proc. Natl. Acad. Sci. 88:3092–96; Kellam et al., 1992, Proc. Natl. Acad.Sci. USA 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559). However, the occurrence of the two consecutive nucleotide changes necessary for the amino acid change at codon 215 may be the most important requirement for the development of resistance (Kellam et al., 1992, Proc. Natl. Acad.Sci. U.S.A. 89:1934–1938; Richman et al., 1991, J. Infect. Dis. 164:1075–1081; Boucher et al., 1992, J. Infect. Dis. 165:105–110). In this study, a subset of 17 patients were tested using a cell culture assay which confirmed that the viruses with a mutation at codon 215 had reduced susceptibility to AZT.

The patients with resistant or sensitive virus in our study had similar CD4 counts at the start of AZT therapy and received AZT for a similar period of time. Therefore, the development of resistance and a mutation at codon 215 could not be attributed to any known pretreatment characteristic. None of our patients developed AIDS during our study period and the patients who developed a mutation in their serum HIV RT did so at a relatively high CD4 count. Thus, advanced stage of HIV disease could not explain why some patients developed a mutation while others did not. Additional characteristics of the patient or virus may explain why one HIV strain develops a mutation and another does not. It has been stated that syncytium-inducing, T-cell tropic isolates in HIV-infected individuals contribute to the CD4 cell decline (Tersmette et al., 1989, Lancet 1:983–985). If an HIV isolate can maintain a high level of replicative events despite the presence of AZT, this virus would have a much greater likelihood of mutation. Treatment with AZT may select both syncytium-inducing and drug resistant virus. Selection of more virulent HIV population under prolonged AZT pressure may explain why some patients experienced a CD4 cell decline in the months after the RT mutation arose.

The present report shows a strong association between the presence of a HIV RT mutation and declining CD4 counts in AZT treated patients. Furthermore, it demonstrates that a HIV mutation known to cause AZT resistance can be detected prior to a decline in CD4 cell number.

Various publications are cited herein that are hereby incorporated by reference in their entirety.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(iii) NUMBER OF SEQUENCES: 5

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA

-continued

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TCCCATTAG TCCTATT 17

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

TCATTGACAG TCCAGCT 17

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

GGATGGAAAG GATCACC 17

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

ATGTTTTTTC TCTGGTGTGG T 21

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

ATGTTTTTTC TCTGGTGTGA A 21

55

What is claimed is:

1. A method of evaluating the effectiveness of anti-HIV therapy of a patient comprising:

(i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent,

(ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR, and

(iii) testing for the presence of HIV-encoding nucleic acid, in the product of the PCR,

in which the absence of detectable HIV-encoding nucleic acid correlates positively with the conclusion that the antiretroviral agent is therapeutically effective.

2. The method of claim 1 in which the HIV primers are SK38 and SK39.

3. The method of claim 1 in which one HIV primer is primer NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2).

4. The method of claim 1 in which one HIV primer is primer A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1).

5. The method of claim 1, 2, 3 or 4 in which the antiretroviral agent is zidovudine.

6. A method of evaluating the effectiveness of anti-HIV therapy of a patient comprising:

(i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent;

(ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and

(iii) testing for the presence of HIV-encoding nucleic acid in the product of the PCR;

in which the presence of detectable HIV-encoding nucleic acid correlates positively with the conclusion that the anti-retroviral agent is therapeutically ineffective.

7. A method of evaluating the effectiveness of anti-HIV therapy of a patient comprising:

(i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent;

(ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and

(iii) testing for the presence of HIV-encoding nucleic acid in the product of the PCR;

in which the presence of detectable HIV-encoding nucleic acid correlates positively with an absolute CD4 count of less than 200 cells per cubic millimeter.

8. A method of evaluating the effectiveness of anti-HIV therapy of a patient comprising:

(i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent;

(ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and

(iii) testing for the presence of HIV-encoding nucleic acid sequence in the product of the PCR;

in which the absence of detectable HIV-encoding nucleic acid correlates positively with an absolute CD4 count of greater than 200 cells per cubic millimeter.

9. A method of evaluating the effectiveness of anti-HIV therapy of a patient comprising

(i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent;

(ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and

(iii) measuring the HIV RNA copy number using the product of the PCR, in which an HIV RNA copy number greater than about 500 per 200 ul of plasma correlates positively with the conclusion that the anti-retroviral agent is therapeutically ineffective.

10. The method of claim 9 in which the HIV primers are SK38 and SK39.

11. The method of claim 9 in which one HIV primer is primer NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2).

12. The method of claim 9 in which one HIV primer is primer A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1).

13. The method of claim 9, 10, 11 or 12 in which the antiretroviral agent is zidovudine.

14. A method of evaluating the effectiveness of anti-HIV therapy of a patient comprising:

(i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent;

(ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and

(iii) measuring the HIV RNA copy number using the product of the PCR, in which an HIV RNA copy number less than about 200 per 200 ul of plasma correlates positively with the conclusion that the anti-HIV agent is therapeutically effective.

15. The method of claim 14 in which the HIV primers are SK38 and SK39.

16. The method of claim 14 in which one HIV primer is primer NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2).

17. The method of claim 14 in which one HIV primer is primer A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1).

18. The method of claim 14, 15, 16 or 17 in which the antiretroviral agent is zidovudine.

19. A method of evaluating the effectiveness of anti-HIV therapy of a patient comprising

(i) collecting one pre-treatment plasma sample from an HIV-infected patient who is about to be treated with an antiretroviral agent;

(ii) collecting a post-treatment plasma sample from the HIV-infected patient after the patient has been treated with the antiretroviral agent;

(iii) amplifying the HIV-encoding nucleic acid in the pre-treatment and post-treatment plasma samples using HIV primers in about 30 cycles of PCR;

(iv) measuring the HIV RNA copy number using the products of the PCRs of step (iii); and

(v) comparing the HIV RNA copy number in pre-treatment and post-treatment plasma samples,

in which a ratio of HIV RNA copy number in pre-treatment and post-treatment plasma samples of greater than about 4 to 1 correlates positively with the conclusion that the anti-HIV agent is therapeutically effective.

20. The method of claim 19 in which the HIV primers are SK38 and SK39.

21. The method of claim 19 in which one HIV primer is primer NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2).

22. The method of claim 19 in which one HIV primer is primer A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1).

23. The method of claim 19, 20, 21 or 22 in which the antiretroviral agent is zidovudine.

* * * * *

39 US006503705B2

(12) **United States Patent**
Kozal et al.

(10) **Patent No.: US 6,503,705 B2**
(45) **Date of Patent: *Jan. 7, 2003**

(54) **POLYMERASE CHAIN REACTION ASSAYS FOR MONITORING ANTIVIRAL THERAPY AND MAKING THERAPEUTIC DECISIONS IN THE TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME**

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(73) Assignee: **Leland Stanford Junior University**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/782,971**

(22) Filed: **Feb. 13, 2001**

(65) **Prior Publication Data**

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(60) Continuation of application No. 09/399,082, filed on Sep. 17, 1999, now abandoned, which is a continuation of application No. 08/470,885, filed on Jun. 6, 1995, now Pat. No. 5,968,730, which is a division of application No. 07/883,327, filed on May 14, 1992, now abandoned.

(51) **Int. Cl.**[7] **C12Q 1/70**; C12Q 1/68; C12P 19/34; C07H 21/04

(52) **U.S. Cl.** **435/5**, 435/6; 435/91.1; 435/91.2; 536/23.1; 536/24.33

(58) **Field of Search** 435/5, 6, 91.1, 435/91.2, 183; 536/23.1, 24.33

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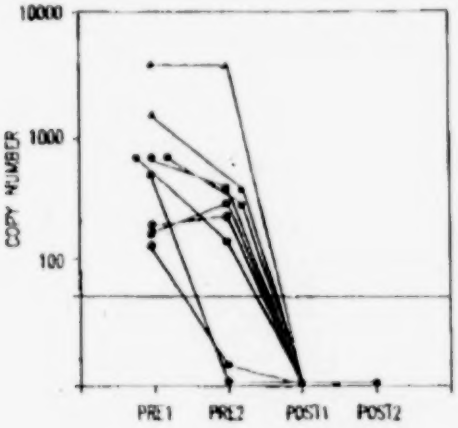
Primary Examiner—B. L. Sisson
(74) *Attorney, Agent, or Firm*—Howrey Simon Arnold & White LLP

(57) **ABSTRACT**

The present invention relates to methods of monitoring, via polymerase chain reaction, the clinical progression of human immunodeficiency virus infection and its response to antiretroviral therapy. According to the invention, polymerase chain reaction assays may be used to predict immunological decline and to identify, at an early stage, patients whose infection has become resistant to a particular antiretroviral drug regimen.

10 Claims, 9 Drawing Sheets



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International Search Report, International Application No. PCT/US93/04560.

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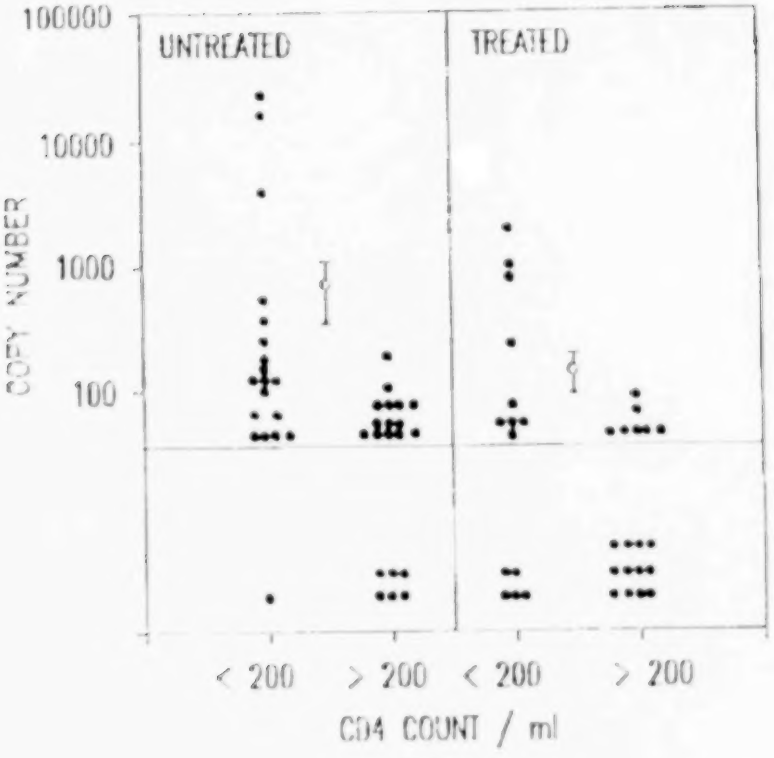
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TREATED
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> 200
< 200
> 200
CD4 COUNT / ml

FIG.1

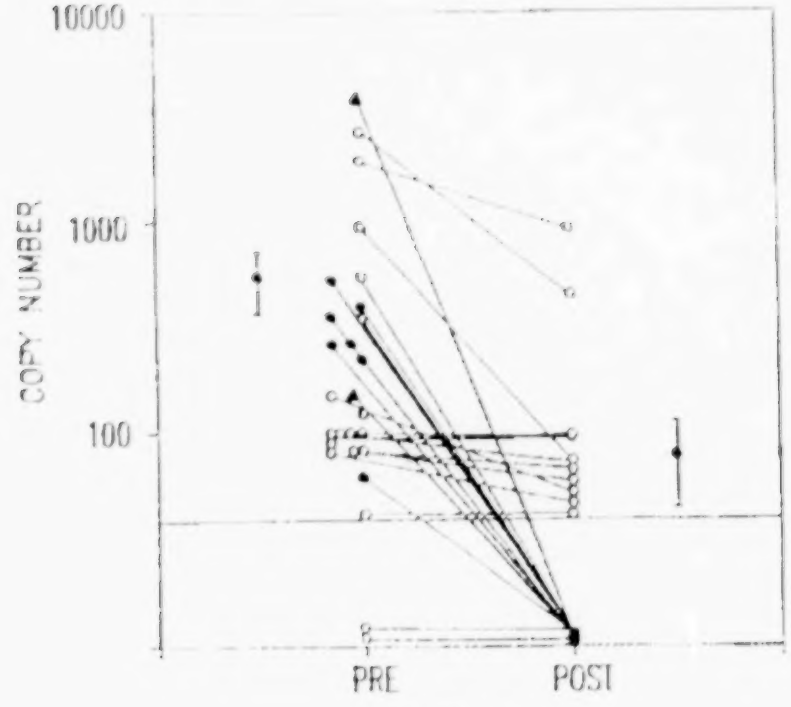
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FIG.2

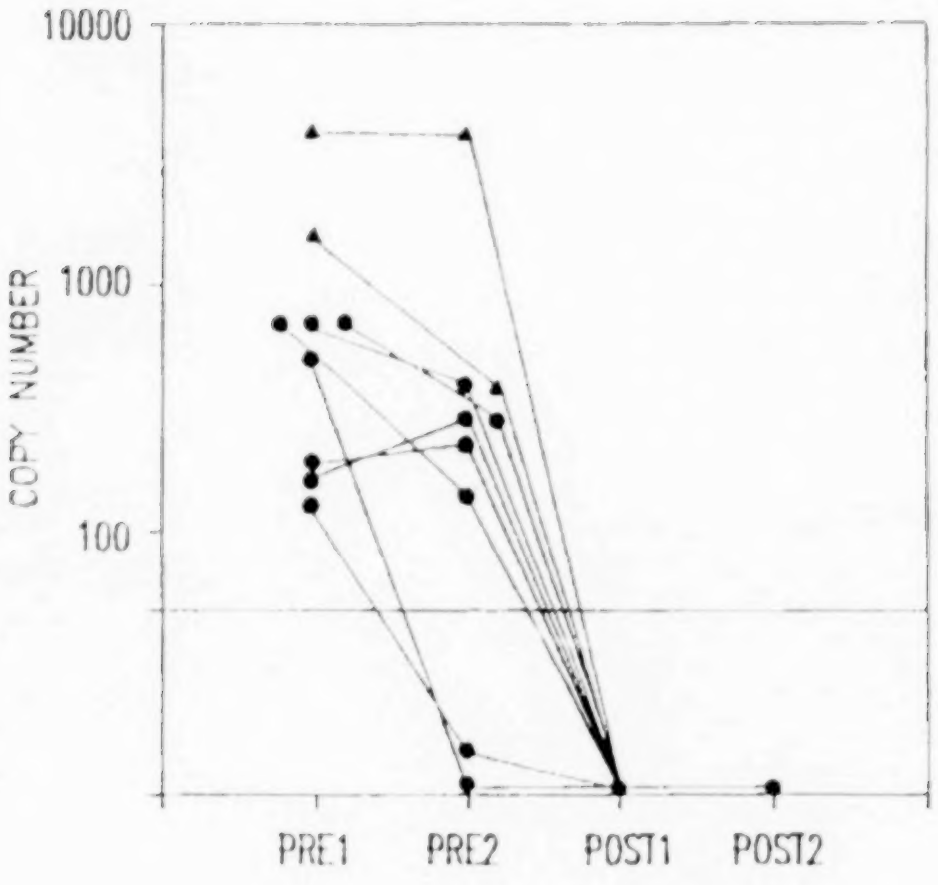
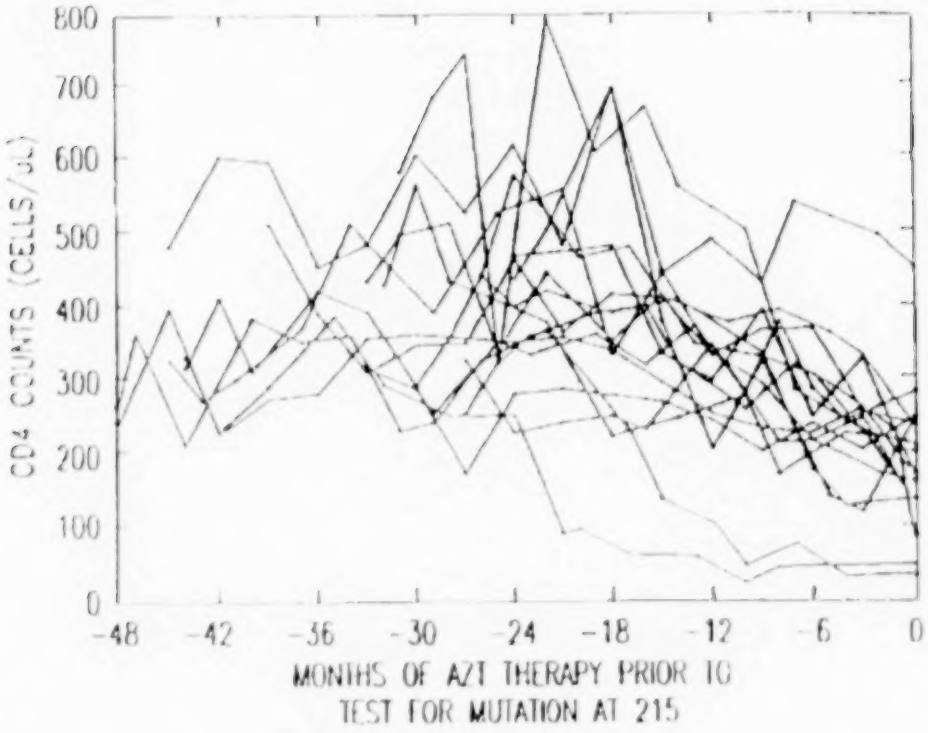


FIG.3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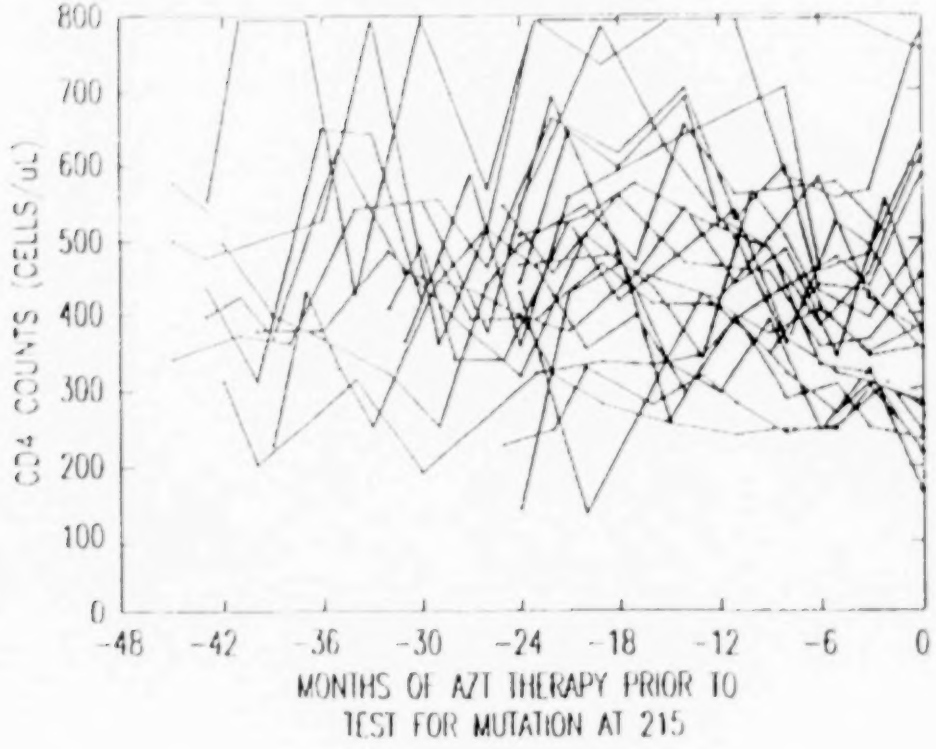
700
600
500
400
300
200
100
0
CD4 COUNTS (CELLS/μL)
-48
-42
-36
-30
-24
-18
-12
-6
0
MONTHS OF AZT THERAPY PRIOR TO
TEST FOR MUTATION AT 215

FIG.4A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CD4 COUNTS (CELLS/μL)
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-6
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MONTHS OF AZT THERAPY PRIOR TO
TEST FOR MUTATION AT 215

FIG.4B

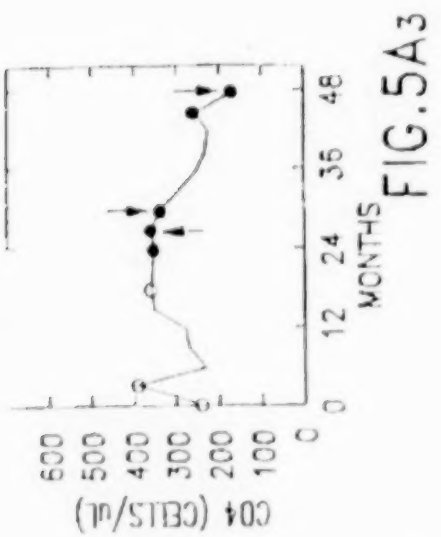


FIG.5A3

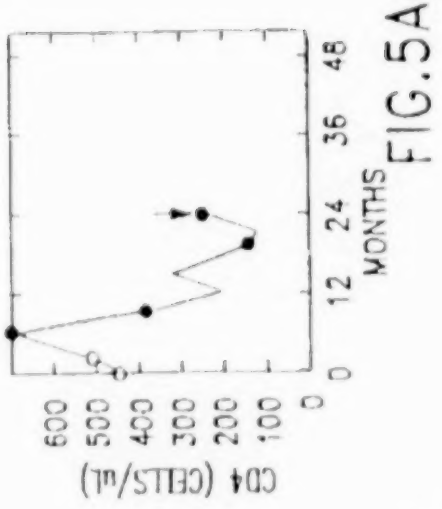


FIG.5A6

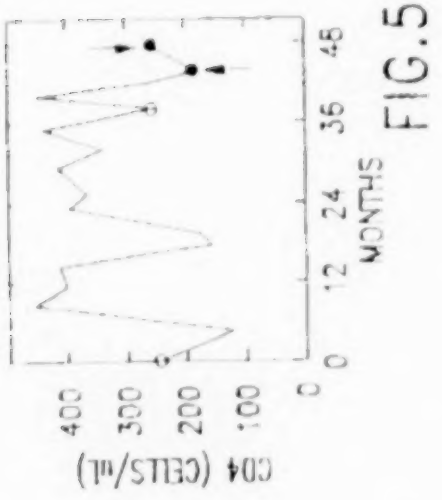


FIG.5A2

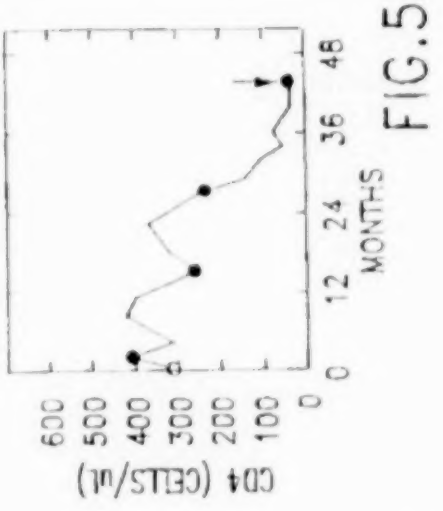


FIG.5A5

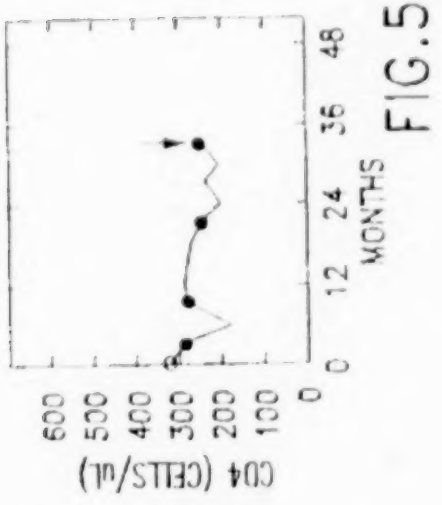


FIG.5A1

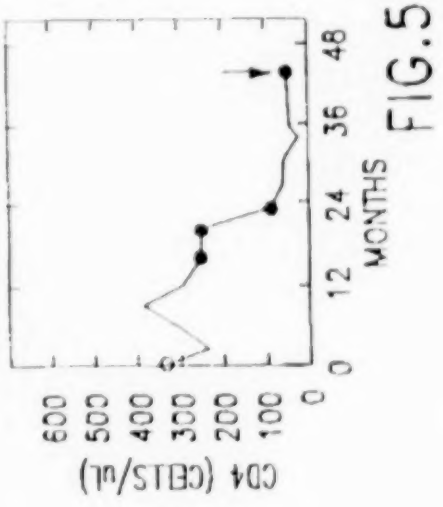


FIG.5A4

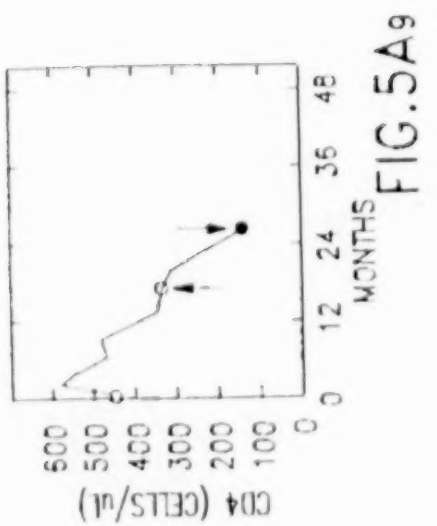


FIG.5A9

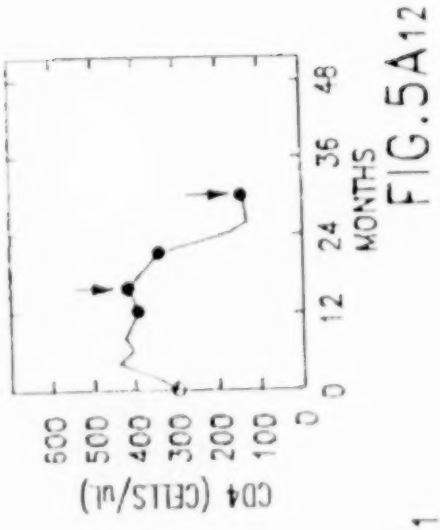


FIG.5A12

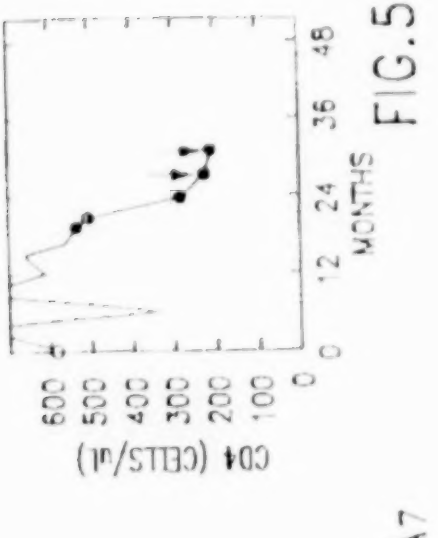


FIG.5A8

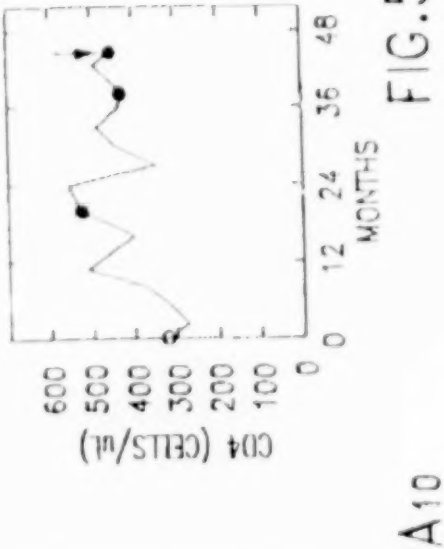


FIG.5A11

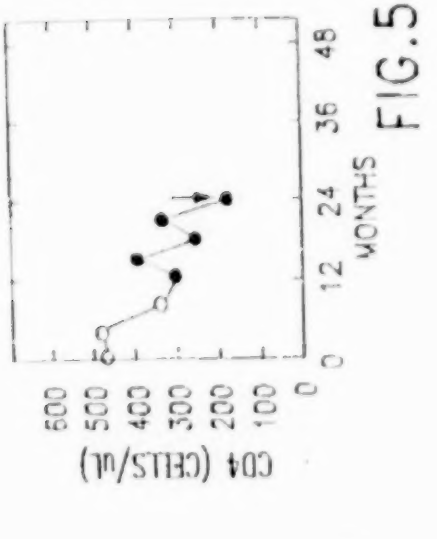


FIG.5A7

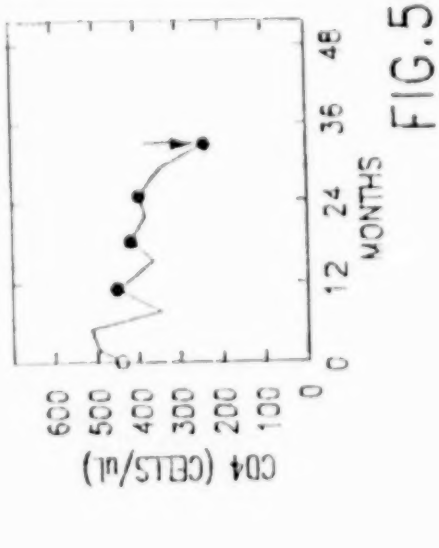


FIG.5A10

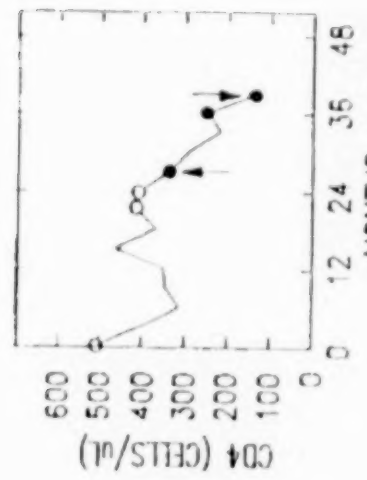


FIG.5A15

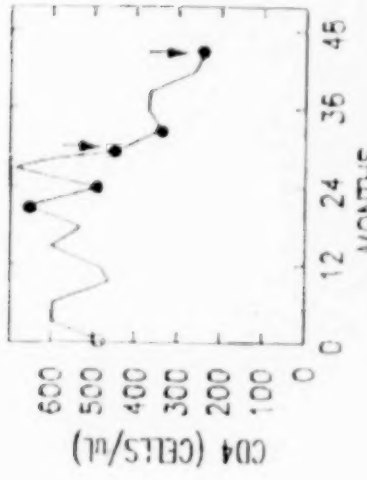


FIG.5A14

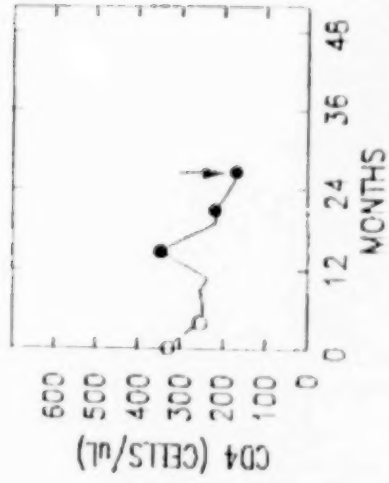


FIG.5A13

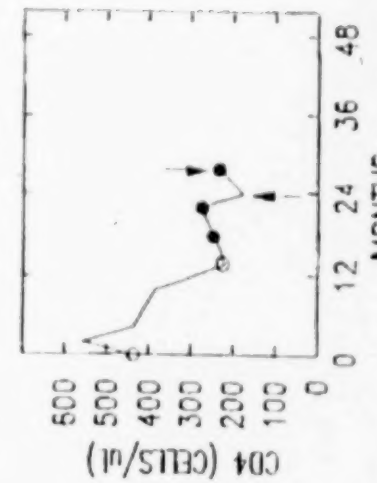


FIG.5A16

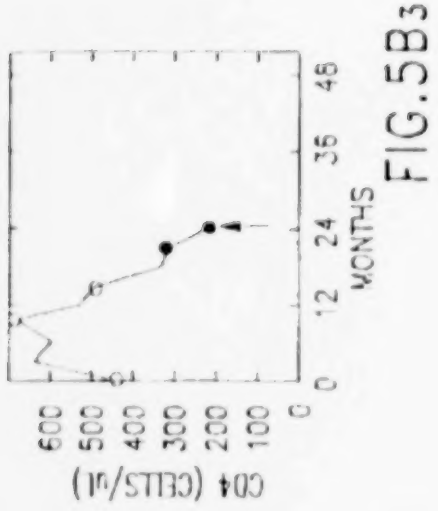


FIG.5B3

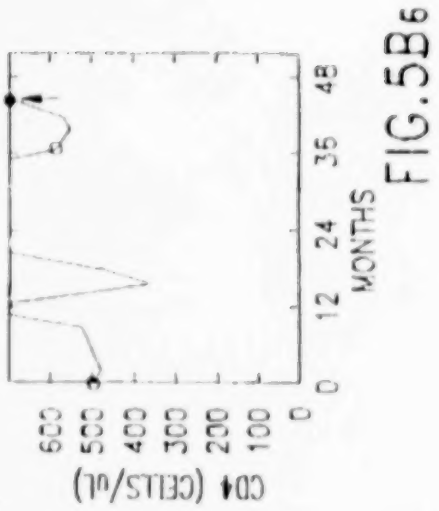


FIG.5B6

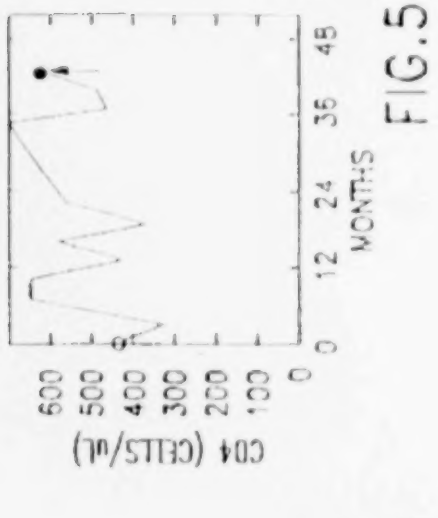


FIG.5B2

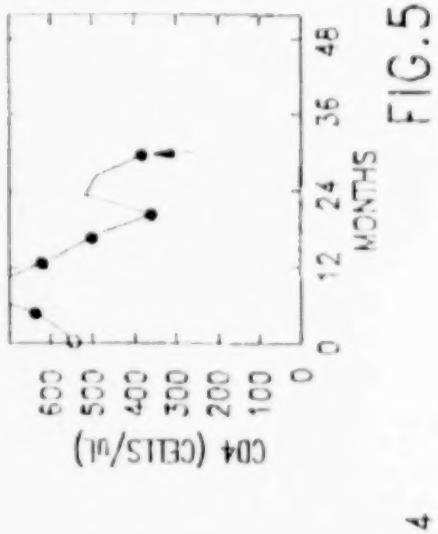


FIG.5B5

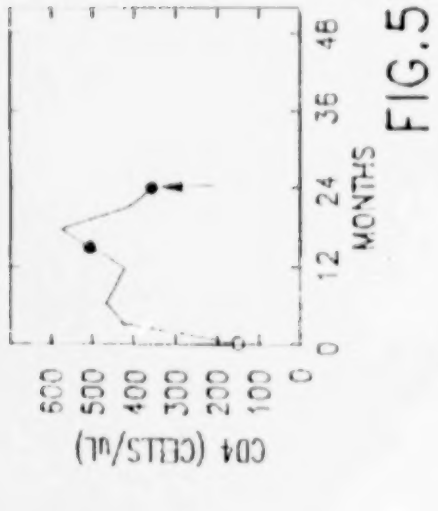
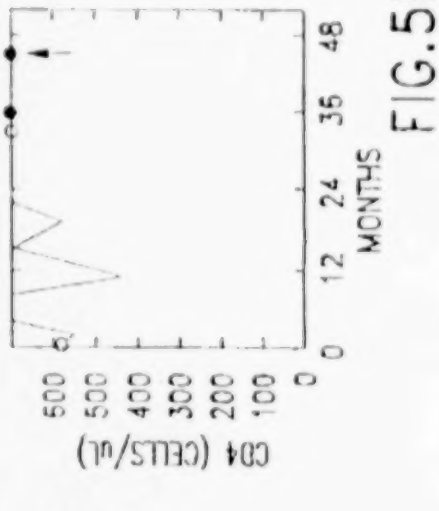


FIG.5B1



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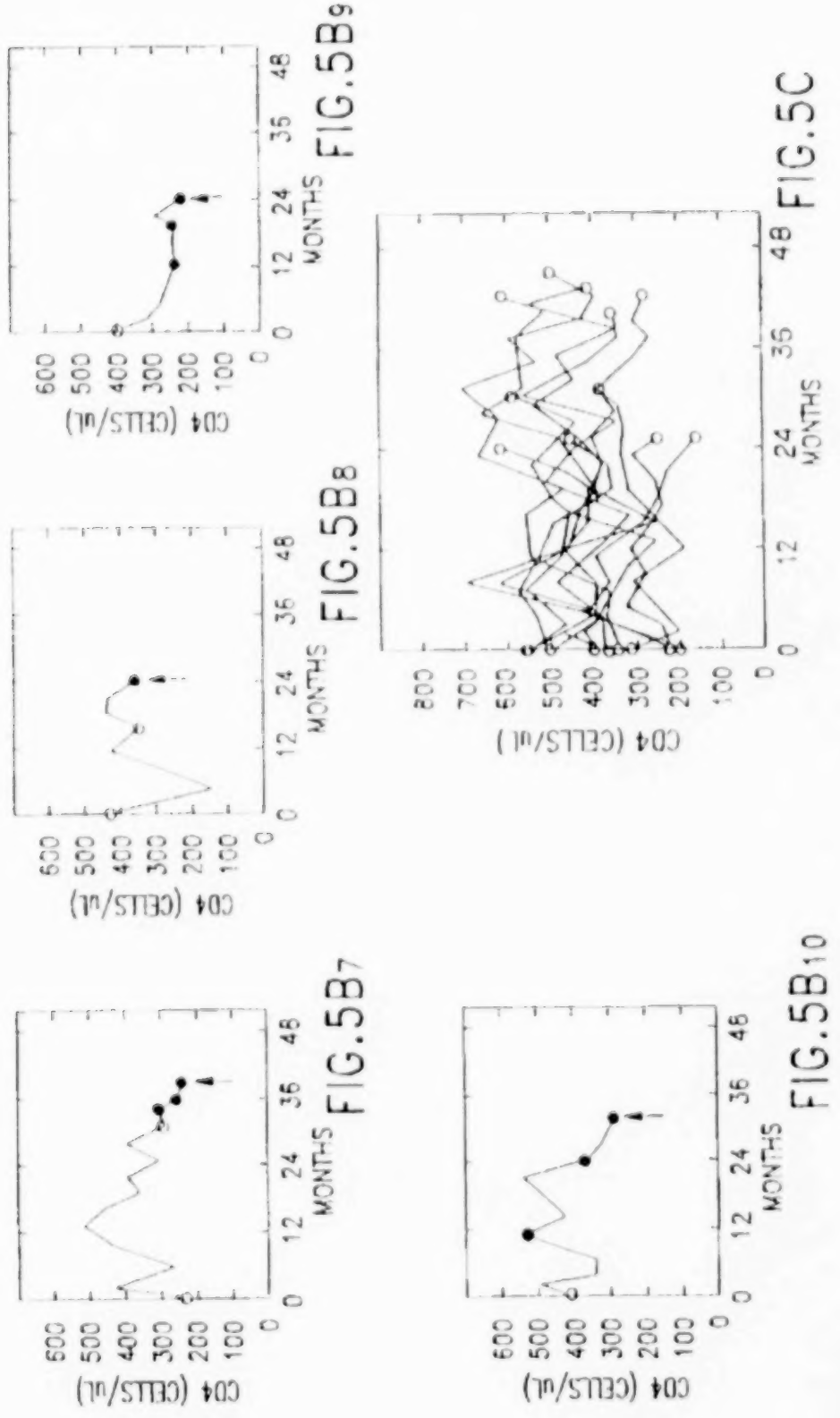


FIG.5B9

FIG.5B8

FIG.5C

FIG.5B7

FIG.5B10

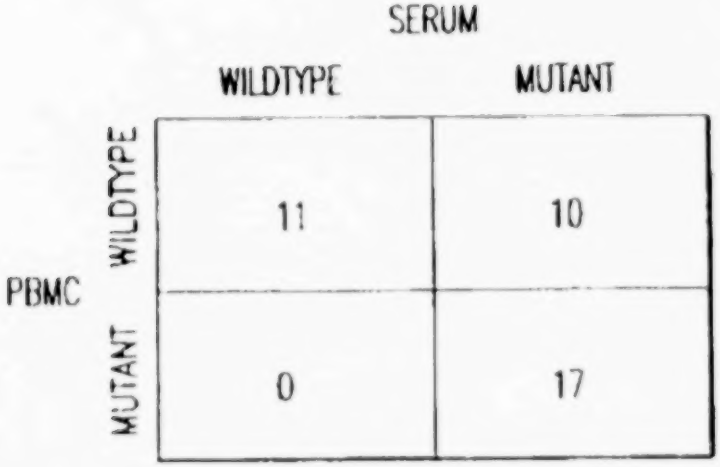
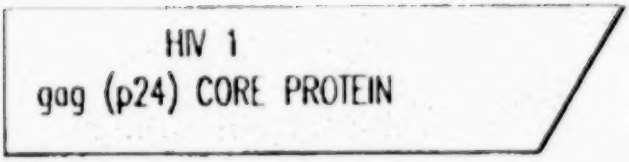


FIG.6



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OLIGO 2
SK 39 5'-TTT GGT CCT TGT CTT ATG TCC AGA ATG C

PROBE
SK 19 5'-ATC CTG GGA TTA AAT AAA ATA GTA AGA
ATG TAT AGC CCT AC

FIG.7

1

POLYMERASE CHAIN REACTION ASSAYS FOR MONITORING ANTIVIRAL THERAPY AND MAKING THERAPEUTIC DECISIONS IN THE TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME

This application is a continuation application of U.S. Ser. No. 09/399,082, filed Sep. 17, 1999, now abandoned, which is a continuation application of U.S. Ser. No. 08/470,855, filed Jun. 6, 1995, now U.S. Pat. No. 5,968,730, which is a divisional application of U.S. Ser. No. 07/883,327 filed May 14, 1992, now abandoned, all of which are incorporated herein by reference in their entirety.

This invention was made with Government support under contracts AI27762-04 and AI27766-07 awarded by the National Institutes of Health. The Government has certain rights in this invention.

INTRODUCTION

The present invention relates to methods of monitoring, via polymerase chain reaction, the clinical progression of human immunodeficiency virus infection and its response to antiretroviral therapy. According to the invention, polymerase chain reaction assays may be used to predict immunological decline and to identify, at an early stage, patients whose infection has become resistant to a particular antiretroviral drug regimen.

BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) isolated from patients treated with zidovudine (AZT) may demonstrate markedly reduced in vitro susceptibility to AZT (Larder et al., 1989, Science 243:1731–1734; Rooke et al., 1989, AIDS 3:411–415; Land et al., 1990, J. Infect. Dis. 161:326–329; Boucher et al., 1990, Lancet 336:585–590; Japour et al., 1991, Proc. Natl Acad. Sci. 88:3092–96; Tudor-Williams et al., 1992, Lancet 339:15–19). This reduced susceptibility has been related to the duration of therapy with AZT and the severity of HIV disease at the time AZT therapy is begun (Richman et al., 1990, J. AIDS 3:743–756). Nucleotide sequence analysis of AZT-resistant HIV strains has revealed a number of mutations in the reverse transcriptase (RT) gene associated with decreased AZT susceptibility (Larder et al., 1989, Science 246:1155–1158; Larder et al., 1991, AIDS 5:137–144; Kellam et al., 1992, Proc. Natl. Acad. Sci. USA 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559; Richman et al., 1991, J. Infect. Dis. 164:1075–1081). Molecular cloning experiments have confirmed that these mutations in the RT gene confer AZT resistance (Larder et al., 1989, Science 246:1155–1158; Larder et al., 1991, AIDS 5:137–144; Kellam et al., 1992, Proc. Natl. Acad. Sci. USA 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559). Of these mutations the one at codon 215 resulting in a single amino acid substitution (Thr→Tyr or Phe) has been shown to be the most common mutation and to have the greatest impact on in vitro susceptibility to AZT (Larder et al., 1991, AIDS 5:137–144; Richman et al., 1991, J. Infect. Dis. 164:1075–1081; Boucher et al., 1992, J. Inf. Dis. 165:105–110).

Several studies have addressed the relationship between in vitro AZT resistance, mutations in the RT gene and clinical disease. Richman and coworkers studied 32 patients with different stages of HIV disease and demonstrated that the development of in vitro AZT resistance was related to the duration of therapy with AZT and to the severity of disease at the time AZT was begun (Richman et al., 1990, J. AIDS 3:743–746). Boucher and coworkers studied HIV P24-antigenemic patients treated with AZT for 2 years. They observed that at 6 months, seven patients with a mutation at codon 215 had a weak, non-statistically significant trend toward lower CD4 counts compared to nine patients who were wild type at codon 215 (Boucher et al., 1990, Lancet 336:585–590). After 2 years nearly all patients had the mutation. Tudor-Williams and coworkers studied HIV isolates from 19 symptomatic children treated with AZT for 9–39 months and showed that in vitro AZT resistance was associated with poor clinical outcome (Tudor-Williams et al., 1992, Lancet 339:15–19). However, adult studies have not shown a precise correlation between the development of in vitro resistance and progression of HIV disease.

2

SUMMARY OF THE INVENTION

The present invention relates to methods of monitoring, via polymerase chain reaction (PCR), the clinical progression of human immunodeficiency virus (HIV) infection and its response to antiviral therapy. It is based, in part, on the discovery that plasma HIV RNA copy number, as measured using PCR, may be used as a sensitive marker of the circulating HIV viral load to assess the therapeutic effect of antiretroviral compounds. In working examples described herein, an increase in plasma HIV RNA copy number was found to correlate with disease progression, and successful antiretroviral therapy was found to correlate with a decline in plasma HIV RNA copy number.

The invention is also based, in part, on the discovery that genetic changes in HIV which confer resistance to antiretroviral therapy may be rapidly determined directly from patient peripheral blood mononuclear cells (PBMC) and/or plasma HIV RNA using a "nested" PCR procedure. In working examples disclosed herein, a mutation at codon 215 of HIV reverse transcriptase (RT) was found to occur in AZT-treated patients which correlated with refractoriness to AZT treatment. The mutation was found in plasma HIV RNA one to eight months before it was detectable in PBMC. The development of the codon 215 mutation in HIV RT was found to be a harbinger of immunological decline, which occurred between six and twelve months after the mutation was detectable in plasma HIV RNA.

In particular embodiments of the invention, PCR assay may be used to monitor the clinical progression of HIV infection in patients receiving antiretroviral therapy. An increase in plasma HIV copy number detected by such an assay would correlate with refractoriness to treatment. If a patient being treated with an antiretroviral therapeutic agent exhibits an increase in plasma HIV RNA copy number, a physician should consider altering the patients treatment regimen. It should be noted that the present invention offers the advantage of being more sensitive in measuring HIV virus than standard methods which measure plasma p24 antigen or infectious virus detectable by culture techniques.

In further embodiments of the invention, PCR assay may be used to detect mutations at codon 215 of HIV RT which correlate with resistance to antiretroviral therapy and which precede immunologic decline by 6–12 months. Once mutation at codon 215 has been detected in a patient undergoing antiretroviral therapy, an alteration in the therapeutic regimen must be considered. The speed at which a modified regimen should be instituted may depend on whether the mutation is present in plasma HIV RNA or PBMC. If the mutation is present in PBMC, a rapid alteration in therapy may be warranted.

In patients suffering from HIV infection, opportunistic infections arising as a result of a compromised immune

system can be rapidly fatal. It is therefore extremely important to strive to avoid deterioration of the immune system in these patients. Because the present invention enables the early prediction of immunological decline, it allows alteration of a patient's therapeutic regimen so as to avoid opportunistic infections, and therefore may be used to promote survival and improve the quality of life of HIV-infected patients.

DESCRIPTION OF THE FIGURES

FIG. 1. Human immunodeficiency virus RNA copy number in 200 μl of plasma from 72 subjects as determined by cDNA gene amplification. Of 39 patients who were not currently receiving antiretroviral therapy, 20 had a CD4 count <200/mm^3 (HIV copy number 1,369±707) and 19 had a CD4 count >200/mm^3 (HIV copy number 44±10). Of 33 subjects who were currently on AZT, 14 had a CD4 count <200/mm^3 (HIV copy number 295±5) and 19 had a CD4 count >200/mm^3 (HIV copy number 16±5). Mean copy number (open circles) of subjects not on therapy was 690±360 as compared to 134±219 for patients currently on AZT ($P<0.05$, independent sample t test).

FIG. 2. Human immunodeficiency virus RNA copy number in plasma from 27 subjects before (pre) and 1 mo after (post) dideoxynucleoside therapy. (○) AZT; (●) AZT+ddI, and (▲) ddI alone. Mean copy number decreased from 540±175 to 77±35 after therapy ($P<0.05$ paired t test).

FIG. 3. Human immunodeficiency virus RNA copy number in plasma from 9 subjects with two samples obtained before initiation of therapy (pre 1 and pre 2) and two samples obtained 1 and 2 mo after commencing therapy (post 1 and post 2). (▲) ddI alone; (●) ddI+AZT.

FIG. 4. Serial CD4 counts in PBMC (cells/μl) of 17 patients in which HIV reverse transcriptase carried a mutation at codon 215 (top) and of 21 patients in which HIV reverse transcriptase was wild type at codon 215 (bottom).

FIG. 5. CD4 cell counts in PBMC from serial time points in 37 patients. ○=wild type sequence in serum specimen, ●=mutant sequence in serum, I=wild type sequence in PBMC, I=mutant sequence in PBMC; A: 16 patients mutant at codon 215 in both serum HIV RNA and PBMC (proviral DNA). B: 10 patients mutant at codon 215 in serum HIV RNA but wild type in their PBMC. C: 11 patients whom remained wild type at codon 215 in their serum HIV RNA and PBMC.

FIG. 6. Relationship of PBMC to serum genotypes in the 38 patients at study endpoint.

FIG. 7. Nucleotide sequences of SK38, SK39, and SK19 (SEQ ID NOS: 6–8).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods of monitoring, via PCR, the clinical progression of HIV infection in patients receiving antiretroviral therapy. For purposes of clarity and not by way of limitation, the detailed description of the invention is divided into the following subsections:

(i) PCR assay of plasma HIV RNA;

(ii) PCR assay of peripheral blood mononuclear cells;

(iii) PCR assay for mutation at codon 215 of HIV reverse transcriptase; and

(iv) utility of the invention.

It should be noted that heparin appears to have an inhibitory effect on gene amplification via PCR. It is therefore desireable to avoid using heparin as an anticoagulant of patient blood samples. If heparin has been used in a sample, the sample may be purified of heparin, for example, by collecting virus by ultracentrifugation.

5.1 PCR Assay of Plasma HIV RNA

According to the invention, it is desireable to avoid degradation of RNA in plasma samples prior to measurement of HIV RNA copy number. Therefore, in preferred embodiments of the invention, guanidinium is added to plasma or serum samples prior to storage at a concentration of about 2.5M and samples are kept frozen at −70° C., with no samples stored for longer than about 3 months. Serum may be used interchangeably with plasma according to the invention.

RNA may be extracted from plasma using standard techniques, such as those set forth in Chomczynski and Sacchi, 1987, Ann. Biochem. 162:156–159. For example, 200 μl of clarified plasma to which 200 μl of 5M guanidinium thiocyanate had previously been added may be extracted with phenol/chloroform and precipitated with isopropanol. The resulting pellet may then be washed in 75 percent ethanol, dried, and brought up into solution in diethylpyrocarbonate-treated glass distilled water.

From plasma RNA, HIV RNA may be transcribed to cDNA using a suitable reverse transcriptase (for example, Moloney murine leukemia virus reverse transcriptase) using standard techiques, such as for example, those set forth in Kawasaki, 1990, in "PCR Protocols: A Guide to Methods and Applications," Innis et al., eds., Academic Press, Berkeley, Calif. pp. 21–27. Any suitable primer for amplification of HIV genomic RNA sequences may be used, including, but not limited to, the oligomers SK38, SK39, and SK19 (FIG. 7) described in Kellog et al., 1990, in "PCR Protocols: A Guide To Methods and Applications," Innis et al., eds., Academic Press, Berkeley, Calif. pp. 337–347. In a preferred embodiment of the invention, HIV cDNA may be amplified as follows: to a 100 μl reaction mixture, cDNA prepared as described supra may be added, together with 50 pmol of primers SK38 and SK39, 10 mM of each dNTP, 10 mM Tris (pH 8.3), 2.5mM $MgCl_2$, 50 mM KCl, and 2.5 U of RECOMBITAQ DNA polymerase (Perkin-Elmer Cetus, Norwalk, Conn.). The mixture may then be overlaid with 50 μl of mineral oil, and tubes containing the reaction may be placed in a DNA thermal cycler (e.g. Perkin Elmer Cetus) for about 30 cycles of amplification with the following program: 95° C./30 seconds, 55° C./30 seconds, and 72° C./60 seconds for denaturation, annealing, and extension, respectively. Negative and positive controls which include both high and low copy number HIV RNA and DNA may be added at each step.

It is important that the number of cycles not exceed 35, and preferably, only about 30 cycles of amplification are used in the PCR. Using a greater number of cycles may detract from the sensivity of the assay.

The copy number of HIV RNA may then be measured by methods known to the skilled artisan. For example, the number of copies of HIV RNA in a patient sample may be quantiated by hybridizing the product of the above PCR with a detectably labeled probe that is complementary to HIV sequence. The amount of signal generated by probe hybridized to PCR product may then be compared to the amount of signal generated by probe hybridized to a known copy number of HIV. Probe may be detectably labeled by an enzyme, a radioisotope, a fluorescent compound, a chromogenic compound, or any other detectably labeled compound.

In a preferred, nonlimiting embodiment of the invention, at least one of the PCR primers may be biotinylated, probe may be labeled with horseradish peroxidase (HRP), and copy number may be evaluated by an enzyme-linked affinity assay as follows. 96-well microplates (Maxisorp; Nunc, Naperville, Ill.) may be coated with 100 μl of a 0.1 mg/ml solution of avidin (Sigma Chemical Co., St. Louis, Mo.) in 50 mM Na_2CO_3 (pH 9.6) overnight at room temperature. Wells may then be washed twice with PBS, and then filled with 300 μl of a blocking solution containing 5X Denhardt's solution, 1% gelatin (Sigma), 250 μl/ml sheared herring sperm DNA (Promega Biotec, Madison, Wis.) at least overnight at 4° C. Immediately before use, the blocking solution may be aspirated from each well and 5 μl of PCR product prepared as described supra (using at least one biotinylated primer) may be added to each well together with 65 μl of a hybridization solution containing 5X saline sodium phosphate EDTA, 5x Denhardt's solution; and 1 pmol of HRP-labeled SK19 HIV gag-specific probe. Because HIV primer was biotinylated, HIV amplified sequences should selectively adhere to the avidin-coated wells, so that a capture and hybridization reaction may be carried out for 1 hour at 42° C. Each well may then be washed about 20 times with PBS containing 0.05% Tween 20™ (polyoxyethylene sorbitan monolaureate), for example, using a Biomek™ 1000 Automated Workstation (Beckman Instruments, Inc., Palo Alto, Calif.). The HRP substrate O-phenylenediamine (Sigma) may then be prepared at 0.6 mg/ml in 0.1 M citrate buffer (pH 5.5) containing 0.03% hydrogen peroxide, and 150 μl of this solution may be added to each well. After about 10 minutes the reaction may be stopped with 1N H_2SO_4 and the optical density of each well measured at 490 nm, for example by the Biomek 1000. A lower level of positivity had been defined as an absorbance of 0.135. This cutoff value was calculated from the mean absorbance obtained from a group of seronegative samples plus three standard deviations. Copy number from subject samples may be determined from the absorbances obtained from a dilution series of an RNA gag gene construct of known copy number (Holodniy et al., 1991, J. Infect. Dis. 163:862-866).

In an alternate preferred, specific embodiment, RNA collected from plasma may be reverse-transcribed by using 500 ng of primer A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1) and 5 units of MuLV RT (Bethesda Research Labs) in 10 μl of amplification buffer (25 mM kCL, 50 mM Tris HCl pH 8.3, 0.1 mg/ml bovine serum albumin, 1.45 mM each of dATP, dGTP, dCTP and dTTP, 1.5 mM $MgCl_2$, and 2.5 U of RNasin (Promega)) for 10 min. at room temperature, then 30 minutes at 42° C. followed by heat inactivation at 95° C. for 5 min. This cDNA may then be amplified by PCR using 250 ng of primer NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2) in a reaction mixture (100 μl) containing the same buffer as above with 0.25 mM of each dNTP and 2.5 U of AMPLITAQ DNA polymerase, using about 30 cycles of 94° C. for 1 min., 45° C. for 1 min, and 72° C. for 2 min, to generate a 768 bp region of the HIV pol gene.

5.2 PCR Assay of Peripheral Blood Mononuclear Cells

Peripheral blood mononuclear cells (PBMCs) may be used fresh or following cryopreservation (e.g. at -190° C.). DNA may be prepared from PBMCs using standard techniques for use in detection of HIV proviral DNA. Any suitable HIV primer oligonucleotide(s) may be used in PCR to detect HIV provirus.

In a preferred, nonlimiting embodiment of the invention, cryopreserved (-190° C.) PBMC may be treated with a lysis buffer (for example, 0.45 percent TWEEN-20™ (polyoxyethylene sorbitan monolaureate), 10 mM Tris HCl pH 8.0, 2.5 mM $MgCl_2$, 50 mM KCl, and 0.1 mg/ml proteinase K) for about two hours at 56° C. and then heat inactivated at 95° C. for 10 minutes. Approximately 1 μg of DNA (20 μl of the PBMC lysate) may be used in the initial PCR amplification with primers A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1) and NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2) with reaction conditions as set forth in Larder et al., 1991, AIDS 5:137-144 to generate a 768 bp region of the HIV pol gene.

5.3 PCR Assay for Mutation at Codon 215 of HIV Reverse Transcriptase

To analyse the changes in codon 215 of the HIV pol gene, a "double" or "nested" PCR procedure was performed using the primers, reagents, and reaction conditions described by Larder et al., 1991, AIDS 5:137-144. Five μl of the 768 bp product generated by PCR with primers A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1) and NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2) and either plasma HIV RNA or PBMC DNA may be used in a second series of nested PCR amplifications using primers that detect wild-type sequence or sequence mutated at codon 215. In preferred, non-limiting embodiments of the invention, the following primers may be used: to detect wild-type sequence primers B (5'-GGATGGAAAGGATCACC-3') (SEQ ID NO:3) and 3 W (3'-TGGTGTGGTCTGTTTTTTGTA-5') (SEQ ID NO:4) and to detect mutants at codon 215, primers B (supra) and 3M (3'-AAGTGTGGTCTGTTTTTTGTA-5') (SEQ ID NO:5). PCR may then be performed as follows. About 1 μl of template may be used per PCR reaction in 100 μl containing 25 mM KCl, 50 mM Tris HCl pH 8.3, 0.1 mg/ml bovine serum albumin (BSA), 0.2 mM each of dATP, dGTP, dCTP and dTTP, 0.25 μl of each oligonucleotide primer, and 1.5 mM $MgCl_2$. Reaction mixtures may be heated at 100° C. for two minutes prior to addition of TAQ DNA polymerase (2.5 U, Perkin-Elmer Cetus, Conn.), overlaid with 100 μl of light mineral oil, and subjected to 30 cycles consisting of a denaturation step (1 minute, 94° C.), primer annealing (30 seconds, 45° C.) and DNA synthesis (30 seconds, 72° C.) using, for example, a Perkin Elmer Cetus DNA thermal cycler. Ten μl of PCR product from each set of "nested" PCR reactions may then be analyzed to determine the presence and intensity of the products. For example, PCR reactions may be analyzed on a 3.0 percent agarose gel with ethidium bromide staining, a portion of a patient sample subjected to "nested" PCR using primers B and 3W may be run in a lane next to another portion of the same patient sample subjected to "nested" PCR using primers B and 3M. A 210 bp PCR product would be expected, if the patient sample contained HIV RT having the codon 215 mutation, the lane carrying primer B/3M PCR product should exhibit a band that is more intense than any corresponding band in the primer B/3W lane. If the patient sample contained only wild type HIV RT, the band in the primer B/3W lane should be more intense than any corresponding band in the primer B/3M lane. Alternatively, if the patient sample contained a mixture of wild type and mutant HIV RT, bands of similar intensities should be in both lanes.

5.4 Utility of the Invention

The present invention relates to methods of monitoring, via PCR, the clinical progression of HIV infection in patients receiving antiretroviral therapy. Techniques described in Sections 5.1 through 5.3 supra, may be used as set forth below.

In one particular embodiment, the present invention provides for a method of evaluating the effectiveness of anti-

retroviral therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent; (ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and (iii) testing for the presence of HIV sequence in the product of the PCR; in which the absence of detectable HIV sequence correlates positively with the conclusion that the antiretroviral agent is therapeutically effective and the presence of detectable HIV sequence correlates positively with the conclusion that the antiretroviral agent is therapeutically ineffective. In further, related, embodiments, the presence of detectable HIV sequence correlates positively with an absolute CD4 count of less than 200 cells/mm^3, and the absence of detectable HIV sequence correlates positively with a CD4 count greater than 200 cells/mm^3. The phrase "correlates positively," as used herein, indicates that a particular result renders a particular conclusion more likely than other conclusions.

In another particular embodiment, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting a plasma sample from an HIV infected patient who is being treated with an antiretroviral agent; (ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and (iii) measuring the HIV RNA copy number using the product of the PCR, in which an HIV RNA copy number greater than about 500 correlates positively with the conclusion that the antiretroviral agent is therapeutically ineffective, and an HIV RNA copy number less than about 200 correlates positively with the conclusion that the antiretroviral agent is therapeutically effective.

In a further embodiment, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting one pre-treatment plasma sample from an HIV-infected patient who is about to be treated with an antiretroviral agent; (ii) collecting a post-treatment plasma sample from the HIV-infected patient after the patient has been treated with the antiretroviral agent; (iii) amplifying the HIV-encoding nucleic acid in the pre-treatment and post-treatment plasma samples using HIV primers in about 30 cycles of PCR; (iv) measuring the HIV RNA copy number using the products of the PCRs of step (iii); and (v) comparing the HIV RNA copy number in pre-treatment and post-treatment plasma samples, in which a ratio of HIV RNA copy number in pre-treatment and post-treatment plasma samples of greater than about 4 to 1 correlates positively with the conclusion that the antiretroviral agent is therapeutically effective.

In additional embodiments of the invention, PCR assay may be used to detect mutations at codon 215 of HIV RT which correlate with resistance to antiretroviral therapy and which precede immunologic decline by 6–12 months. Accordingly, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent; and (ii) determining (for example, using "nested" PCR) whether the plasma sample comprises nucleic acid encoding HIV RT having a mutation at codon 215, in which the presence of the mutation correlates positively with immunologic decline of the patient within a six to twelve month period. Under such circumstances, the HIV virus infecting the patient has become, via the mutation, resistant to the antiretroviral agent. It therefore maybe desirable after detecting the mutation, to either increase the dosage of antiretroviral agent, change to another antiretroviral agent, or add one or more additional antiretroviral agents to the patient's therapeutic regimen. For example, if the patient was being treated with zidovudine (AZT) when the mutation arose, the patient's therapeutic regimen may desirably be altered, within about a six to twelve month period of the mutation's occurrence, by either (i) changing to a different antiretroviral agent, such as dideoxyinosine (ddI) and stopping AZT treatment; or (ii) increasing the dosage of AZT; or (iii) adding another antiretroviral agent, such as ddI, to the patient's therapeutic regimen. The effectiveness of the modification in therapy may be evaluated, as set forth above, by monitoring the HIV RNA copy number. A decrease in HIV RNA copy number correlates positively with the effectiveness of a treatment regimen.

Because the mutation at the 215 codon appears first in plasma HIV RNA and later in PBMC proviral DNA, once the mutation is detected in proviral DNA, the treatment regimen is desirably modified with haste in order to avoid immune decline. Accordingly, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting PBMC from an HIV-infected patient who is being treated with an antiretroviral agent; and (ii) determining whether the PBMC comprise proviral HIV DNA which comprises a mutation at codon 215, in which the presence of the mutation correlates positively with immunologic decline of the patient within a 4–11 month period (because, as discussed in Section 7, infra, a mutation in serum HIV RNA was found to precede the mutation in proviral DNA by 1–8 months). Once the mutation is detected in proviral DNA, immune decline becomes even more imminent, and alteration of the patient's therapeutic regimen is desirable.

When immune decline is heralded by the increase in HIV RNA copy number and/or the presence of the mutation at codon 215, in addition to altering the patient's antiretroviral therapy, it may also be desirable to treat the patient prophylactically for opportunistic infections, using antifungal, antibiotic, and/or antiparasitic medications.

Antiretroviral agent, as used herein, includes any known antiretroviral agent including, but not limited to, dideoxynucleosides. In preferred embodiments of the invention the antiretroviral agent is AZT. Resistance to certain antiretroviral agents, including AZT, is associated with a mutation at codon 215. Resistance to other antiretroviral agents, such as ddI, is associated with a mutation at codon 74. The present invention provides for analogous techniques in which the effectiveness of antiretroviral therapy is monitored by determining whether plasma HIV RNA or PBMC contain a mutation at codon 74 of HIV RT, in which a mutation at that locus may augur immunological decline and may warrant a modification of antiretroviral therapy.

One preferred, non-limiting, specific embodiment of the invention is as follows: A method of evaluating the effectiveness of AZT therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with AZT; (ii) amplifying the HIV-encoding RNA in the plasma sample by converting the RNA to cDNA and amplifying HIV sequences using HIV primers in about 30 cycles of PCR; and (iii) testing for the presence of HIV sequence in the product of the PCR, in which the absence of detectable HIV sequence correlates positively with the conclusion that AZT is therapeutically effective and the presence of detectable HIV sequence correlates positively with the conclusion that AZT is therapeutically ineffective. In most preferred embodiments, the HIV primers used comprise NE1 (supra), SK38 and/or SK39 (supra), and/or the presence of HIV sequence is detected using an enzyme-

linked assay (e.g., a horseradish peroxidase based assay). Similar embodiments in which the HIV copy number is measured are also provided for.

Another preferred, non-limiting, specific embodiment of the invention is as follows: A method of evaluating the effectiveness of AZT therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with AZT, (ii) amplifying the HIV-encoding RNA in the plasma sample by converting the RNA to cDNA and amplifying HIV sequences using HIV primers that result in a PCR product that comprises that portion of the RT gene that contains the 215 codon (e.g. primer NE1, supra), (iii) performing "nested" PCR using primers that result in PCR products that reflect the presence of wild type (e.g. primers B and 3W, supra) or 215 codon mutant (e.g. primers B and 3M, supra), and (iv) determining, via the products of "nested" PCR, the presence or absence of a mutation at codon 215 of the HIV RT, in which the presence of the mutation correlates positively with immunologic decline of the patient within a six to twelve month period. An analogous method may be used in which the patient sample is PBMC, and the presence of a mutation is proviral DNA is determined.

EXAMPLE

Reduction in Plasma Human Immunodeficiency Virus Ribonucleic Acid after Didcoxynucleoside Therapy as Determined by the Polymerase Chain Reaction

6.1 Materials and Methods

6.1.1 Patients

After informed consent was obtained, whole blood samples were collected by venipuncture in the presence of acid citrate dextrose as an anticoagulant. A single plasma sample was collected from 39 HIV antibody-positive subjects who were not receiving antiretroviral therapy at the time of collection and from 33 HIV antibody-positive subjects who were currently on and had received AZT for a minimum of 3 mo.

Two plasma samples were collected from an additional 27 subjects before and 1 month after initiation of dideoxy nucleoside therapy. 18 of these subjects received 500 mg/d of AZT orally. Seven subjects received a combination of zidovudine (150–600 mg/d) and 2',3'-dideoxyinosine (ddI) (134–500 mg/d). Two patients received 500 mg/d of ddI alone (see Table 1 for individual subject characteristics). Finally, nine of these subjects had two plasma samples taken 1–3 wk before initiating antiretroviral therapy and two plasma samples taken 1 and 2 mo after commencing therapy. Plasma was separated within 4 h by centrifugation at 500 g for 10 min. A second centrifugation was performed on the plasma at 500 g for 30 min, to remove any cellular material. 200 μl of plasma was then mixed with 200 μl of a solution containing 5 M guanidinium thiocyanate, vortexed briefly, and stored at −70° C. until further use. All samples were assayed within 3 mo. of collection. To decrease variance, all specimens to be compared from the same subject were run in the same assay.

6.1.2 Extraction of RNA from Plasma

RNA was extracted from plasma by the method described in Chomczynski et al., 1987, Ann. Biochem. 162:156–159. Briefly, 200 μl of clarified plasma to which 200 μl of 5 M guanidinium thiocyanate had previously been added was extracted with phenol/chloroform and precipitated with isopropanol. The resulting pellet was then washed in 75% ethanol, dried, and brought up in diethylpyrocarbonate treated, glass distilled water.

6.1.3 Reverse Transcription and Amplification of cDNA

HIV RNA was transcribed to cDNA using Moloney murine leukemia virus reverse transcriptase (Bethesda Research Laboratories, Gaithersburg, Md.) by the method described in Kawasaki, 1990, "In PCR Protocols: A Guide to Methods and Applications" pp. 21–27, M. A. Innis, D. H. Gelfand, J. J. Sninsky, and T. J. White, eds. Academic Press, Berkeley, Calif. Oligomers used for amplification included SK38, SK39, and SK19 (Kellog et al., 1990, "In PCR Protocols: A Guide to Methods and Applications," pp. 337–348, M. A. Innis, D. H. Gelfand, J. J. Sninsky, and T. J. White, eds. Academic Press, Berkeley, Calif.). Biotinylation of SK38 and horseradish peroxidase (HRP) labeling of probe SK19 were prepared as described in Levenson et al., 1990, "In PCR Protocols: A Guide to Methods and Applications," pp. 99–112 M. S. Innis, D. H. Gelfand, J. J. Sninsky, and T. J. White, eds. Academic Press, Berkeley, Calif. Amplification of HIV cDNA was carried out as follows: to a 100-μl reaction mixture was added the cDNA, 50 pmol of primers SK38 and SDK39, 10 mM of each dNTP, 10 mM Tris (pH 8.3), 2.5 mM $MgCl_2$, 50 mM KCl, and 2.5 U of RECOMBITAQ DNA polymerase (Perkin-Elmer Cetus, Norwalk, Conn.). The mixture was then overlaid with 50 μl of mineral oil. Tubes were placed in a DNA thermal cycler (Perkin-Elmer Cetus) for 30 cycles of amplification with the following program: 95° C./30 s, 55° C./30 s, and 72° C./60 s for denaturation, annealing, and extension, respectively. Negative and positive controls which included both high and low copy number HIV RNA and DNA were added at each step.

6.1.4 Enzyme linked Affinity Assay

To detect and quantitate PCR product, 96-well microplates (Maxisorp, Nunc, Naperville, Ill.) were coated with 100 μl of a 0.1 mg/ml solution of avidin (Sigma Chemical Co., St. Louis, Mo.) in 50 mM Na_2CO_3 (pH 9.6) overnight at room temperature. Wells were then washed twice with PBS. Wells were then filled with 300 μl of a blocking solution containing 5X Denhardt's solution, 1% gelatin (Sigma), 250 μl/ml sheared herring sperm DNA (Promega Biotec, Madison, Wis.) at least overnight at 4° C. Immediately before use, the blocking solution was aspirated from each well and 5 μl PCR product and 65 μl of a hybridization solution, containing 5X saline sodium phosphate EDTA, 5X Denhardt's solution, and 1 pmol of HRP-labeled SK19 HIV gag specific probe was added to each well. A capture and hybridization reaction was then carried out in the well for 1 h. at 42° C. The 96-well microplate was then placed in a Biomek™ 100 Automated Workstation (Beckman Instruments, Inc., Palo Alto, Calif.) where wells were washed 20 times with BPS containing 0.05% Tween-20™ (polyoxyethylene sorbitan monolaureate). The HRP substrate O-phenylenediamine (Sigma) was prepared at 0.6 mg/ml in 0.1 M citrate buffer (pH 5.5) containing 0.03% hydrogen peroxide. 150 μl of this substrate solution was added to each well. After 10 min. the reaction was stopped with 1 NH_2SO_4 and the optical density of each well measured at 490 nm by the Biomek 1000. A lower level of positivity had been defined as an absorbance of 0.135. This cutoff value was calculated from the mean absorbance obtained from a group of seronegative samples plus three standard deviations. Copy number from subject samples were determined from the absorbances obtained from a dilution series of an RNA gag genic construct of known copy number described in Holodniy et al., 1991, J. Infect. Dis. 163:862–866. The lower level of sensitivity in this assay was 40 copies of HIV gag genic RNA.

6.1.5 Plasma HIV Culture and P24 Antigen Assay

Quantitative HIV plasma microculture was performed according to the method described in Ho et al., 1989, N. Engl. J. Med. 321:1621–1625. P24 antigen was detected by an antigen capture assay by a method provided by the supplier (Abbott Laboratories, North Chicago, Ill.)

6.1.6 Statistical Analysis

Sample optical density was converted to copy number and analyses performed on samples expressed as RNA copy number/200 μl of plasma. A t test of independent samples was used in analysis of subject who did not receive antiretroviral therapy compared to subjects who were receiving AZT. A t test of paired samples was used to analyze paired plasma data and CD4 counts from subjects pre- and post-therapy. All t tests were two tailed. A Fisher's exact test or chi square test were used for analysis of proportion where appropriate. Statistical significance was defined as $P<0.05$.

6.2 Results

72 subjects were evaluated in a cross-sectional study of HIV disease to determine plasma HIV RNA copy number by PCR. The results are presented in FIG. 1. 39 subjects who were not currently receiving antiretroviral therapy and 33 subjects who were receiving AZT were evaluated. Untreated subjects were more likely to have a positive signal than treated subjects (32 of 39 vs. 16 of 33, respectively, P 0.008, chi square). In the 39 subjects who were not currently receiving therapy, the mean plasma HIV RNA copy number was 690±360 (mean±SEM) per 200 μl of plasma, while the 33 subjects who had been receiving AZT therapy had a mean copy number of 134±219 ($P<0.05$). Mean CD4 count for each group was 316±45 and 300±37, respectively (P=NS).

Subgroups were then analyzed with respect to CD4 count. Among those with <200 CD4 cells, untreated subjects were more likely to have positive signal than treated subjects (18 of 19 vs. 9 of 14, $P<0.04$, Fisher's exact test). Among those with >200 CD4 cells, 14 of 20 untreated subjects vs. 7 of 19 treated subjects had a detectable signal (P=NS, Fisher's exact test). Untreated subjects with CD4 count <200/mm^3 had a mean RNA copy number of 1,369±707 and mean CD4 count of 73±17, untreated subjects with CD4 >200/mm^3 had a mean RNA copy number of 44±10 and mean CD4 count of 547±45; treated subjects with CD4 counts <200/mm^3 had a mean RNA copy number of 295±5 and mean CD4 count of 115±13, and treated subjects with CD4 counts >200/mm^3 had calculated mean RNA copy number of 16±5 (which is below the level of detection of this assay and would be interpreted as negative) and mean CD4 count of 437±41.

27 additional subjects were then evaluated before and 1 mo after initiation of dideoxynucleoside therapy. Clinical parameters of the subjects are presented in Table 1. PCR results are presented in FIG. 2. Results show that plasma HIV RNA copy number fell from 540±175 to 77±35 after therapy ($P<0.05$, paired t test). Mean CD4 count increased from 399±24 to 442±25 after 4 wk of therapy ($P<0.006$, paired t test).

TABLE 1

Clinical Parameters and PCR Analysis of Plasma HIV RNA from 27 Patients

Patient No.	Antiviral treatment	Pre/post CD4	Pre/Post HIV RNA
1*	AZT[1]	641/561	106/80
2*	AZT	541/651	130/0
3	AZT	840/834	550/0
4	AZT	452/462	100/77
5*	AZT	379/415	87/57
6*	AZT	428/408	40/42
7	AZT	422/345	94/94
8	AZT	420/402	0/0
9	AZT	<32/532	93/65
10	AZT	430/430	105/52
11	AZT	429/404	123/50
12	ddI + AZT[3]	280/220	526/0
13	AZT	323/320	70/45
14	AZT	320/456	95/95
15	AZT	353/387	301/0
16	ddI + AZT[3]	309/369	300/0
17	ddI + AZT[3]	337/398	260/0
18	ddI[4]	328/310	966/0
19	ddI + AZT[3]	383/491	245/0
20	AZT	404/413	0/0
21	AZT	280/450	958/72
22	ddI + AZT[3]	292/344	60/0
23	AZT	530/595	2769/457
24	ddI[4]	222/370	3944/0
25	AZT	568/132	2014/925
26	DDI + AZT[5]	367/473	217/0
27	DDI + AZT[5]	310/369	4.96/0

*Remote history of AZT use

[1]AZT dose 500 mg/d unless otherwise stated

[3]AZT 300 mg/d + ddI 334 mg/d

[4]ddI 500 mg/d

[5]AZT 600 mg/d + ddI 500 mg/d

[5]AZT 150 mg/d + ddI 134 mg/d

Finally, 9 of the 27 subjects had two samples taken before initiation of therapy and two samples taken 1 and 2 months after commencing therapy. The results are presented in FIG. 3. When two pretherapy time points were analyzed for constancy of signal, results show that mean copy number for each pretherapy time point was 945±377 and 643±392.

Two subjects had a second pretherapy sample which was negative. When both pretherapy copy number values were compared to post therapy values, plasma HIV RNA copy number fell from 794±274 to <40 (which is below the lower level of detection in this assay) after 1 and 2 mo of therapy ($P<0.05$, paired t test). Mean CD4 count increased from 314±165 to 378±25 ($P<0.05$, paired t test).

Plasma culture was performed on fresh material obtained from the initial pretreatment sample for 23 of 27 of these patients only 7 of 23 were plasma virus positive by culture (from 1 to 100 tissue culture infective dose/ml). All 23 of these patients were positive by PCR (>40 copies/200 μl). In addition, a p24 antigen test was performed on all 27 pre-treatment samples. Only 2 of 27 had detectable p24 antigen present (>30 pg/ml).

6.3 Discussion

The results presented here demonstrate that plasma HIV RNA can be detected and quantified by copy number in the majority of patients infected with HIV. In addition, plasma HIV RNA copy number may be used as a marker of circulating HIV viral load to assess treatment effect of antiretroviral compounds including dideoxynucleoside compounds. We initially conducted a survey to determine whether treatment or degree of immunologic impairment, based on CD4 count, affected plasma HIV RNA copy number. Untreated patients as a group had higher copy numbers than treated patients. Untreated patients with <200 CD4 cells/mm^3 had a higher mean copy number than patients with >200 CD4 cells/mm^3. Likewise, treated

patients with <200 CD4 cells/mm^3 had higher copy numbers than patients with >200 CD4 cells/mm^3, indicating that patients with more advanced HIV disease have higher circulating copy numbers than asymptomatic patients, and that the antiretroviral benefit seen in patients with higher CD4 counts may be waning.

To assess the short-term impact of antiretroviral therapy on patients, 27 patients were evaluated before and 1 mo after initiation of AZT, ddI, or combination therapy. As CD4 counts increased after 1 mo of therapy, HIV RNA copy number fell significantly. However, the response of individual subjects was variable. 16 of 27 subjects had a marked decrease in copy number and 11 of 27 did not. Because the majority of subjects received AZT alone, it was not possible to assess any differences between AZT, ddI, or combination regimens.

Finally, nine subjects had two baseline time points taken in the 3 wk before treatment, followed by two monthly samples posttreatment. Pretreatment signal was constant in 7 of 9 subjects, and 2 subjects had discordant samples, i.e., one was positive and one was negative. This could be related to real changes in circulating HIV RNA, or introduced during sample collection, handling, or the assay. However, pretherapy and posttherapy samples were run in the same assay and so were subject to all of the same reaction conditions. When sample positivity was considered in relation to therapy, 16 of 18 pretherapy samples had a positive signal vs. 0 of 18 posttherapy samples ($P<0.001$, chi square) showing suppression of HIV RNA copy number with treatment.

Currently there is no standard method to assess circulating viral load in all HIV-infected patients. Plasma viremia, measured by quantitative microculture, can identify and quantify infectious virus in 50–100% of patients, principally those with advanced stages of HIV disease, low CD4 counts, and p24 antigenemia (Ho et al., 1989, N. Engl. J. Med. 321:1621–1625; Coombs et al., 1989, J. Virol. Methods 26:23–21; Ehrnst et al., 1988, N. Engl. J. Med. 324:961–964). Many patients with >200 CD4 cells/mm^3 do not have detectable infectious plasma viremia. This may be due to an absence of circulating infectious virus, virus which is neutralized by specific antibody, or the insensitivity of culture techniques. The results presented here indicate that the majority of patients with >200 CD4 cells/mm^3 do not have plasma p24 antigen or infectious virus detectable by culture techniques. In the studies described herein, it appears that virus undetectable by culture methods was detectable by PCR methods.

Attempts have been made to assess HIV viral load in patients by molecular techniques, mainly by quantitative PCR of HIV proviral DNA in circulating mononuclear cells or cell-free virion-associated RNA in plasma. Published data suggest that the number of cells infected with HIV increases with advancing disease and that HIV proviral DNA content increases as well. We and others have shown a decrease in HIV proviral DNA with dideoxynucleoside therapy over time (Aoki et al., 1990, AIDS Res. Hum. Retroviruses 6:1331–1339). This was not the case in another published small series (McElrath et al., 1991, J. Clin. Invest. 87:27–30).

We have shown that HIV RNA could be quantified in serum and that copy number increased with disease progression (Holodniy et al., 1991, J. Infect. Dis. 163:862–866). Plasma HIV RNA has been shown to be present before and after seroconversion with quantitative decreases occurring after seroconversion (Hewlett et al., 1988, J. Clin. Immunoassay 11:161–164). The recent report by Daar et al. (Daar et al., 1991, N. Engl. J. Med. 324:961–964), showed a decrease in both plasma viremia and proviral DNA from PBMC, coinciding with seroconversion after acute infection. In one report, plasma HIV RNA levels fell with passive immunoglobulin therapy, suggesting a therapy-based response in circulating HIV RNA load (Karpas et al., 1990, Proc. Natl. Acad. Sci. USA 87:7613–7617). Ottman and colleagues have been successful in detecting HIV RNA in plasma from 95% of patients evaluated (Ottman et al., 1991, J. Virol. Methods 31:273–284). They also studied a group of patients who were receiving AZT to determine whether there was any therapeutic impact on HIV RNA signal. 24 of 25 patients who were receiving AZT had detectable signal. However, methodological differences in that study vs. the present study may have contributed to the differences noted between them. First, Ottman et al. used an ultracentrifugation step to sediment virus, enhancing virion-associated RNA recovery. Second, 40 cycles of amplification after reverse transcription were performed, which would certainly increase the sensitivity of such an assay to successfully detect HIV RNA in virtually all patients. Although sensitivity is increased with increased cycle number, thus detecting signal in virtually all patients, the ability to show the quantitative changes demonstrated here with 30 cycles of amplification is lost.

We have previously shown in serum that quantitative serum cultures were negative in the majority of patients with >200 CD4 cells/mm^3 (Holodniy et al. 1991, J. Infect. Dis. 163:862–866). In the current study, 23 plasma samples were evaluated by culture and PCR. All had detectable plasma HIV RNA by PCR< but only seven were plasma HIV-culture positive. Other published experience comparing plasma HIV culture and PCR of HIV RNA from plasma is lacking. Ottman et al. tested only two patients, both of whom were positive in both assays. Coyle et al. reported that 14 of 20 patients had positive plasma cultures and 12 of 20 patients had detectable HIV RNA in plasma, but no information was given regarding concordance or discordance of samples (Coyle et al., 1990, Clin. Res. 38:778a (Abstr.)).

The type of plasma sample and method of processing and storage were found to be very important. The type of anticoagulant used for sample collection can affect detection of plasma RNA. We have previously shown that plasma collected in the present of heparin does not allow detection of signal because of an inhibitory effect of heparin on gene amplification (Holodniy et al., 1991, J. Clin. Microbiol. 29:676–679). Although Coyle et al. (1990, Clin. Res. 38:778a (Abstr.)) found detectable signal from plasma collected in the presence of heparin, an ultracentrifugation step preceding RNA analysis lead to removal of most of the heparin from the enzyme-mediated assay system. However, no comparison experiments among anticoagulants were performed to demonstrate any attenuation of signal obtained in the presence of heparin.

Because of our concern for RNA degradation during specimen storage and freeze thawing, we decided to store fresh plasma at −70° C. in the presence of guanidinium and process samples within 3 mo of collection. Samples were stored in guanidinium for RNAase inhibition. Preliminary data from our laboratory would suggest that plasma HIV RNA signal decays with time in the absence of this RNA stabilizer.

In summary, we have shown that plasma HIV RNA copy number can be quantitated by PCR and does decrease with dideoxynucleoside therapy. The nonisotopic, microplate-based format presented here makes it possible to process multiple patient samples with replicates in a single amplification and assay run.

EXAMPLE

Relationship of a Mutation in the HIV Reverse Transcriptase Gene to Decline in CD4 Lymphocyte Numbers in Long Term AZT Recipients

7.1 Materials and Methods

7.1.1 Study Population

Cryopreserved PBMC and serum from 40 participants in AIDS Clinical Trial Group (ACTG) protocols 019 (30 patients) and 016 (10 patients) at Stanford University Medical Center AIDS Clinical Trial Unit were used in this study. Patients at enrollment in these studies were AZT naive, had >200 CD4 cells/μl and had few (016) or no symptoms (019) referable to HIV infection. They were subsequently treated with AZT for 2 to 4 years. The most common dosage was 500 mg per day. Approximately one third of patients received either 1200 mg or 1500 mg per day during the initial part of their therapy, but were changed to 500 mg per day when lower doses were found to be as effective but less toxic than higher doses (Fischl et al., 1990, N. Engl. J. Med. 323:1009-1014; Volberding et al., 1990, N. Engl. J. Med. 322:941-949). All samples were obtained from the patients while they were on the protocols and thus no patient developed an AIDS defining diagnosis.

7.1.2 CD4 Cell Counts

CD4 cell counts were obtained approximately every three months on each patient. All counts were performed at Stanford's ACTG-qualified cytofluorometry lab. Samples were stained with monoclonal antibodies to CD3, CD4, and CD8. The absolute CD4 count was calculated by multiplying the percent CD4 by the total lymphocyte count.

7.1.3 PBMC Preparation

Cryopreserved (−190° C.) PBMC were treated with a lysis buffer (0.45% TWEEN 20™ (polyoxyethylene sorbitan monolaurate), 10 mM Tris HCl pH 8.0, 2.5 mM $MgCl_2$, 50 mM KCl, and 0.1 mg/ml proteinase K) for 2 hours at 56° C. and then heat inactivated at 95° C. for 10 min. Approximately 1μg of DNA (20 μl of the PBMC lysate) was used in the initial PCR amplification with primers A(5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1) and NE1(5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2) with reaction conditions as described in Larder et al., 1991, AIDS 5:137–144 to generate a 768bp region of the HIV pol gene.

7.1.4 Serum HIV RNA Preparation

Cryopreserved (−70° C.) serum was thawed and then 350 μl of sera was added to 350 μl of solution D (Chomczynski et al., 1987, Anal. Biochem. 162:156–159) (guanadinium thiocyanate+2-mercaptoethanol) and vortexed. RNA was then extracted with phenol and chloroform and precipitated with ethanol as described in Chomczynski et al., 1987, Anal. Biochem. 162:156-15918. HIV RNA was then reverse transcribed to cDNA by using 500 ng of primer A and 5 units of murine leukemia virus (MuLV) reverse transcriptase (Bethesda Research Labs) in 10 μl of amplification buffer (25 mmol/L KCl, 50 mmol/L Tris HCl Ph 8.3, 0.1 mg/ml bovine serum albumin, 1.45 mmol/L each of dATP, dGTP, dCTP and dTTP, 1.5 mmol/L $MgCl_2$, 2.5 units of RNasin (Promega)) for 10 min at room temperature, then 30 min at 42° C. followed by heat inactivation at 95° C. for 5 min. This cDNA was then amplified by PCR using 250 ng of primer NE1 in a reaction mixture (100 μl) containing the same buffer as above with 0.25 mmol/L of each dNTP and 2.5 units of AMPLITAQ DNA polymerase (Perkin Elmer Cetus). This reaction mixture underwent 30 cycles of 94° C. for 1 min, 45° C. for 1 min and 72° C. for 2 min to generate a 768bp region of the HIV pol gene.

7.1.5 PCR Analysis of HIV Reverse Transcriptase Gene

To analyze the changes in codon 215 of the HIV pol gene, a "double" PCR procedure was performed using the primers, reagents, and reaction conditions described in Larder et al., 1991, AIDS 5:137–144. Five μl of the 768 bp product generated by PCR with primers A and NE1 was used in a second series of nested PCR amplifications using primer B and 3W to determine if a wild type sequence was present, or B and 3M to determine if a mutant sequence was present (primer sequences as set forth supra and in Larder et al., 1991, AIDS 5:137–144). Samples were run with negative, positive and reaction mixture controls. Ten μl of PCR product from each of the second set of PCR reactions were analyzed on a 3.0% agarose gel with ethidium bromide staining. PCR products were considered to have a mutant or wild type sequence by the method described by Boucher et al. (1990, Lancet 336:585–590, 1992, J. Infect. Dis. 165:105–110) and Larder et al., 1991, AIDS 5:137–144: a sample was considered to contain the wild type sequence at codon 215 if amplification with the primers B and 3W resulted in a 210 bp PCR product of highest intensity; a sample was considered to contain a mutant sequence at codon 215 if amplification with the primers B and 3M resulted in a 210 bp PCR product of highest intensity. The sample was considered to have a mixture of wild type and mutant sequences if amplification occurred with both primers 3M and 3W resulting in PCR products of similar intensity. If a mixture was detected by PCR then that sample was included in the mutant group in our statistical analysis.

7.1.6 AZT Sensitivity Assay

Patient PBMC were cocultured with mitogen-stimulated PBMC from healthy HIV-seronegative donors. Supernatants from these cultures were collected and frozen when the HIV P24 antigen concentration exceeded 10,000 pg/ml. 30–100 $TCID_{50}$ (50% tissue culture infectious dose) of virus stock was used to infect one million donor PBMC pretreated with different concentrations of AZT (0.0 uM, 0.005 uM, 0.05 uM, 0.5 uM, 5.0 uM). After 7 days, P24 antigen was measured in the cell free supernatant from the cultures with and without zidovudine. The concentration of AZT required to inhibit P24 production by 90% (IC_{90}) as compared to the drug free cultures was determined by nonlinear regression analysis (Chou et al., 1984, Adv. Enzyme Regulation 22:27–55). In this assay, the IC_{90}s from AZT-naive patients ranged from 0.002 μM to 0.038 μM AZT.

7.1.7 Statistical Analysis

All comparisons between the patients with mutant and wild type strains were performed using the student's t-test. The calculations on the IC_{90}s determined by the zidovudine sensitivity assay were performed using the $\log_{10}$ transformed IC_{90} (i.e. geometric means were used rather than arithmetic means).

7.2 Results

7.2.1 PCR Analysis of Codon 215 in PBMC

Proviral DNA was detected by nested PCR in the PBMC of 38 of 40 patients after a mean 34 month treatment period. The two patients in whom proviral DNA could not be detected had high CD4 counts at the time their PBMC were analyzed (729 and 676 cells/μl). PCR amplification of the PBMC from 17 of 38 patients (45%) yielded a 210 bp product with the mutant primer, indicating the presence of a mutation at codon 215 (Thr to Tyr or Phe). The PBMC from 21 of 38 patients (55%) demonstrated amplification product only with the wild type primer (a 210 bp product) indicating the presence of Thr at codon 215.

The mean length of therapy and starting CD4 counts for the two groups were similar (Table 2). However, the 17

patients with a mutation at codon 215 of HIV RT in PBMC proviral DNA had a 50% decrease in their absolute CD4 count between the time they began therapy (378 cells/μl) and the end of the study (189 cells/μl). The 21 patients with a wild type sequence at codon 215 experienced a mean 11% increase in their absolute CD4 count between the time they began therapy (397 cells/μl) and the end of the study (424 cells/μl). The post-treatment CD4 percentages of the two groups of patients were also significantly different (25% in patients with wild-type sequence vs 14% in patients with a mutation in RT at codon 215) (Table 2). The CD4 counts at each time point for each patient are shown in FIG. 4

TABLE 2

CORRELATION OF PATIENT CD4 COUNT CHANGES WITH PCR ANALYSIS OF CODON 215 OF HIV REVERSE TRANSCRIPTASE IN PBMC

	Wildtype	Mutant	p
Number of patients	21	17	
Months of AZT	33 ± 8	35 ± 7	0.4
Starting CD4 measurements			
Absolute CD4 (cells/μl)	397 ± 124	378 ± 96	>0.5
CD4 %	26 ± 8	25 ± 6	>0.5
CD4 measurements at a time of PCR analysis			
Absolute CD4 (cells/μl)	424 ± 210	189 ± 98	<0.0001
CD4 %	25 ± 9	14 ± 6	0.0001

7.2.2 PCR Analysis of Codon 215 in HIV RNA from Serum

Serial PBMC samples from earlier time points were available on 8/40 patients; however, serial serum samples from earlier time points were available on 37/40 patients. In these 37 patients, 135 serum samples were tested for the presence of a codon 215 mutation. In 87% of these samples (117), reverse transcribed cDNA could be detected by PCR. Fifteen of the 18 sera that were negative by PCR had been previously subjected to multiple freeze-thaws and therefore could be falsely negative. As all patients were AZT-naive, they were assumed to be wild type at codon 215 at the start of AZT therapy.

Twenty-six of the 37 patients developed a mutation in their HIV RNA. This included the 16 who were also mutant in their PBMC at the end of the study period (FIG. 5A), and ten patients who were wild type in their PBMC but mutant in serum HIV RNA at the end of the study period (FIG. 5B). The time preceding the occurrence of the 215 mutation in their serum ranged from 2 to 44 months of therapy. Among these 26 patients, the mean CD4 count at the start of therapy was 398±139 cells/μl and their mean CD4 count at the time of first detection of a codon 215 mutation in their serum was 444±206 cells/μl. Nineteen of the 26 patients with a codon 215 mutation in their serum had follow-up CD4 counts at least 12 months after the mutation was first detected. In these 19 patients, there was a mean decrease of 100±116 CD4 cells/μl (25% decline) at six months and a mean decrease of 170±121 CD4 cells/μl (40% decline) at 12 months.

The 11 patients who remained wild type in their serum over the entire 34 month period of zidovudine therapy had an increase of 7±92 CD4 cells/μl (2% increase), (FIG. 5C). The mean CD4 count at the start of therapy for the patients who later developed a mutant in their serum was 398±139 cells/μl and this was not significantly different than the starting CD4 counts for those patients who remained wild type (397±115 cells/μl, p>0.5). The average length of therapy for both groups was 34 months.

7.2.3 Serum Virus Compared to PBMC Provirus

At the final evaluation of the 38 patients after a mean 34 months of zidovudine, 11 patients were wild type in both serum and PBMC, 17 were mutant in both serum and PBMC, and 10 patients had a mutation in their serum but remained wild type in their PBMC FIG. 6. Eight of the 17 patients with a mutation in proviral DNA at the end of the study period had at least one PBMC sample available from an earlier time point. In these eight patients, a mutation in serum HIV RNA preceded the mutation in proviral DNA by 1-8 months. The findings in these 8 patients and in the 10 patients who were wild type in their PBMC but mutant in their serum shows that detection of the serum mutation precedes detection of the mutation in PBMC. In no instance, did a mutation in patient's PBMC precede its appearance in serum.

7.2.4 AZT Sensitivity Results Determined by Cell Culture

In vitro AZT susceptibility testing was performed on 17 of 38 patients using a different aliquot of the same post-treatment PBMC that were used for the PCR analysis. The geometric mean of the IC_{50}s of eight patients with the wild type form at 215 was 0.04 μm AZT (range: 0.02-0.28 μm); the geometric mean IC_{50} of nine patients with a mutation at codon 215 was 0.41 μm AZT (range: 0.03-8.0 μM; p=0.002).

7.3 Discussion

As an increasing number of HIV infected individuals are offered early treatment with AZT, the significance of drug resistant virus has become an important question. In the present study we found a strong correlation between the presence of a mutation at codon 215, which is linked to AZT resistance and an accelerated decline in CD4 cell number. The patients we studied all began taking AZT when their CD4 cell numbers were relatively high and before the onset of AIDS. We observed that the 17 patients with a mutation at codon 215 in proviral DNA in their PBMC experienced a mean 50% decrease in their CD4 count between the time that they began therapy and the time that their cells were analyzed for mutations. The 21 patients who were wild type at codon 215 in their proviral DNA at the end of treatment experienced a mean 11% increase in their CD4 count during the same time period.

Patient cells were only available during the last year of the study. However, by extracting and reverse transcribing HIV RNA from patient's serum specimens we were able to detect codon 215 mutation at earlier time points. The patients in our study with and without a mutation in serum HIV had similar starting CD4 counts (397±115 vs. 398±139, p>0.5) and similar lengths of therapy (34 months in both groups). Yet we found that those patients who develop a mutation in HIV RNA had a subsequent 40% decline in their CD4 cells over the next 12 months. The patients who remained wild type in their serum had a 2% increase in their CD4 cells over 34 months of therapy.

These results show that genetic changes in the virus which confer drug resistance can be rapidly determined directly form patient PBMC and HIV RNA in patients serum using a nested PCR procedure. By using PCR we were able to detect viral nucleic acid in 90% of PBMC samples and 87% of serum samples. Techniques which require culturing HIV from PBMC or serum may select HIV subpopulations with greater tropism for certain cells (Kusumi et al., 1992, J. Virol. 66:875-885; Meyerhans et al., 1989, Cell 58:901-910). This may complicate the analysis of the clinical significance of AZT resistance detected by phenotypic assays.

Earlier clinical studies focused on AZT resistance in patients with initially low CD4 cell counts or who were at

high likelihoid of disease progression. Furthermore, these studies tested HIV isolates which had been passaged in culture. In contrast, in this study we did not select patients at high likelihood for disease progression but instead we included all patients who remained on AZT for at least 2 years and who had high CD4 counts at the beginning of the study; codon 215 mutations in serum virus occurred early in treatment. The mean CD4 count at the first appearance of the mutation was higher than the CD4 count at the start of therapy (444 vs. 398 cells/μl). This suggests that mutation of the reverse transcriptase gene is not dependent upon low CD4+ T cells. On the other hand, we also found that a large percentage of patients remained wild type at codon 215 and phenotypically sensitive to AZT despite almost 3 years of therapy. This may be because our patients were less advanced in their disease or that by using PCR instead of coculture we were able to include patients whose virus might not have grown in culture. These results also suggest that the PBMC may not be the initial source of mutant virus, as evidenced in 18 of our patients where the serum HIV RNA mutation preceded that in PBMC by many months. The source of the mutant HIV detected in serum may be cells in lymphatic, central nervous system or reticuloendothial sites.

The significance of specific mutations in the RT gene with respect to AZT resistance has been defined in patient isolates as well as through molecular cloning experiments (Larder et al., 1989, Science 246:1155–1158; Larder et al., 1991, AIDS 5:137–144; Kellam et al., 1992, 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559). Of the four mutations first reported to be associated with AZT resistance (codons 67, 70, 215, 219), the mutation at codon 215 has been shown to be the most commonly occurring and to have the greatest impact on susceptibility. This impact on AZT susceptibility will vary depending on whether or not additional mutations are present (Larder et al., 1989, Science 246:1155–1158; Larder et al., 1991, AIDS 5:137–144; Kellam et al., 1992, 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559; Richman et al., 1991, J. Infect. Dis. 164:1075–1081; Boucher et al., 1992, J. Infect. Dis. 165:105–110). Recent sequencing studies of clinical isolates suggest that there are additional mutations in the RT gene that may contribute to AZT resistance (Japour et al., 1991, Proc. Natl. Acad. Sci. 88:3092–96; Kellam et al., 1992, Proc. Natl. Acad. Sci. USA 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559). However, the occurrence of the two consecutive nucleotide changes necessary for the amino acid change at codon 215 may be the most important requirement for the development of resistance (Kellam et al., 1992, Proc. Natl. Acad. Sci. U.S.A. 89:1934–1938; Richman et al., 1991, J. Infect. Dis. 164:1075–1081; Boucher et al., 1992, J. Infect. Dis. 165:105–110). In this study, a subset of 17 patients were tested using a cell culture assay which confirmed that the viruses with a mutation at codon 215 had reduced susceptibility to AZT.

The patients with resistant or sensitive virus in our study had similar CD4 counts at the start of AZT therapy and received AZT for a similar period of time. Therefore, the development of resistance and a mutation at codon 215 could not be attributed to any known pretreatment characteristic. None of our patients developed AIDS during our study period and the patients who developed a mutation in their serum HIV RT did so at a relatively high CD4 count. Thus, advanced stage of HIV disease could not explain why some patients developed a mutation while others did not. Additional characteristics of the patient or virus may explain why one HIV strain develops a mutation and another does not. It has been stated that syncytium-inducing, T-cell tropic isolates in HIV infected individuals contribute to the CD4 cell decline (Tersmette et al., 1989, Lancet 1:983–985). If an HIV isolate can maintain a high level of replicative events despite the presence of AZT, this virus would have a much greater likelihood of mutation. Treatment with AZT may select both syncytium-inducing and drug resistant virus. Selection of more virulent HIV population under prolonged AZT pressure may explain why some patients experienced a CD4 cell decline in the months after the RT mutation arose.

The present report shows a strong association between the presence of a HIV RT mutation and declining CD4 counts in AZT treated patients. Furthermore, it demonstrates that a HIV mutation known to cause AZT resistance can be detected prior to a decline in CD4 cell number.

Various publications are cited herein that are hereby incorporated by reference in their entirety.

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What is claimed is:

1. A method of evaluating the effectiveness of anti-HIV therapy of an HIV-infected patient comprising:

a) collecting statistically significant data useful for determining whether or not a decline in plasma HIV RNA copy numbers exists after initiating treatment of an HIV-infected patient with an antiretroviral agent by:

(i) collecting more than one plasma sample from the HIV infected patient at time intervals sufficient to ascertain the existence of a statistically significant decline in plasma HIV RNA copy numbers;

(ii) amplifying the HIV-encoding nucleic acid in the plasma samples using HIV primers via PCR for about 30 cycles;

(iii) measuring HIV RNA copy numbers using the products of the PCR of step (ii);

(iv) comparing the HIV RNA copy numbers in the plasma samples collected during the treatment; and

b) evaluating whether a statistically significant decline in plasma HIV RNA copy numbers exists in evaluating the effectiveness of anti HIV therapy of a patient.

2. The method of claim 1 in which the HIV primers are SK38 and SK39.

3. The method of claim 1 in which one HIV primer is primer NE1 (5'-TCATTGACAGTCCAGCT-3')(SEQ ID NO:2).

4. The method of claim 1 in which one HIV primer is primer A (5'-TTCCCATTAGTCCTATT-3')(SEQ ID NO:1).

5. The method of claim 1 in which the antiretroviral agent is zidovudine.

6. The method of claim 1, wherein the presence of a statistically significant decline in plasma HIV RNA copy number correlates positively that the antiretroviral agent is therapeutically effective.

7. The method of claim 1 wherein the absence of a statistically significant decline in plasma HIV RNA copy numbers correlates positively that the antiretroviral agent is therapeutically ineffective.

8. A method of evaluating the effectiveness of anti-HIV therapy of a patient comprising:

(i) collecting a pre-treatment plasma sample from the HIV-infected patient who is about to be treated with an antiretroviral agent;

(ii) collecting a plasma sample after initiation of treatment with an antiretroviral agent and at a time interval sufficient to ascertain the existence of a statistically significant decline in plasma HIV RNA copy numbers;

(iii) amplifying the HIV-encoding nucleic acid in the plasma samples using HIV primers via PCR for about 30 cycles;

(iv) measuring HIV RNA copy numbers using the products of the PCR of step (iii);

(v) comparing the HIV RNA copy numbers in the plasma samples collected in the pre-treatment plasma sample and the plasma sample(s) collected after initiation of the treatment; and

(vi) evaluating whether a statistically significant decline in plasma HIV RNA copy numbers exists in evaluating the effectiveness of anti-HIV therapy of a patient.

9. The method of claim 8, wherein comparing the HIV RNA copy numbers of step (v) further comprises determining a ratio of HIV RNA copy numbers in the pre-treatment and the post-treatment plasma samples, wherein the ratio being greater than about 7 to 1 correlates positively with the conclusion that the antiretroviral agent is therapeutically effectiveness.

10. The method of claim 7, wherein comparing the HIV RNA copy numbers of step (v) further comprises determining a ratio of HIV RNA copy numbers in the pre-treatment and the post-treatment plasma samples, wherein the ratio being greater than about 4 to 1 correlates positively with the conclusion that the antiretroviral agent is therapeutically effectiveness.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,503,705 B2
DATED : January 7, 2003
INVENTOR(S) : Thomas C. Merigan, David A. Katzenstein and Mark Holodniy

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [75], Inventors, delete "**Michael J. Kozal**, Menlo Park, CA (US);"
Item [74], *Attorney, Agent or Firm*, please replace "Howrey Simon Arnold & White, Ltd." with -- Howrey Simon Arnold & White, LLP --

Column 12,
Line 48, please insert a period after "patients" and capitalize "only" to read as follows:
-- patients. Only 7 of 23 were plasma virus positive by culture --

Signed and Sealed this

Seventeenth Day of June, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,503,705 B2
APPLICATION NO. : 09/782971
DATED : January 7, 2003
INVENTOR(S) : Thomas C. Merigan, David A. Katzenstein and Mark Holodniy

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the claims:

Column 24, line 30, delete "The method of claim 7" and insert --The method of claim 8--.

Signed and Sealed this

Fifteenth Day of April, 2008

JON W. DUDAS
Director of the United States Patent and Trademark Office

64 US007129041B2

(12) **United States Patent**
Merigan et al.

(10) **Patent No.: US 7,129,041 B2**
(45) **Date of Patent: *Oct. 31, 2006**

(54) **POLYMERASE CHAIN REACTION ASSAYS FOR MONITORING ANTIVIRAL THERAPY AND MAKING THERAPEUTIC DECISIONS IN THE TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME**

(75) Inventors: **Thomas C. Merigan**, Portola Valley, CA (US); **David A. Katzenstein**, Menlo Park, CA (US); **Mark Holodniy**, Mountain View, CA (US)

(73) Assignee: **The Board of Trustees of the Leland Stanford Junior University**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 77 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/321,162**

(22) Filed: **Dec. 16, 2002**

(65) **Prior Publication Data**

US 2003/0118986 A1 Jun. 26, 2003

Related U.S. Application Data

(60) Division of application No. 09/782,971, filed on Feb. 13, 2001, now Pat. No. 6,503,705, which is a continuation of application No. 09/399,082, filed on Sep. 17, 1999, now abandoned, which is a continuation of application No. 08/470,885, filed on Jun. 6, 1995, now Pat. No. 5,968,730, which is a division of application No. 07/883,327, filed on May 14, 1992, now abandoned.

(51) **Int. Cl.**

C12Q 1/70	(2006.01)
C12Q 1/68	(2006.01)
C12P 19/34	(2006.01)
C12M 1/34	(2006.01)
C07H 21/04	(2006.01)

(52) **U.S. Cl.** 435/5; 435/6; 435/91.2; 435/183; 435/287.2; 536/23.1; 536/23.72; 536/24.33

(58) **Field of Classification Search** 435/5, 435/6, 91.2, 183, 287.2; 536/23.1, 23.72, 536/24.33

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,968,730 A * 10/1999 Merigan et al. 435/5
6,503,705 B1 * 1/2003 Kozal et al. 435/5

OTHER PUBLICATIONS

Complaint, dated Oct. 14, 2005, as filed in *The Board of Trustees of The Leland Stanford Junior University v. Roche Molecular Systems, Inc.*, Case No. C 05 04158 JCS, pending in United States District Court for the Northern District of California.

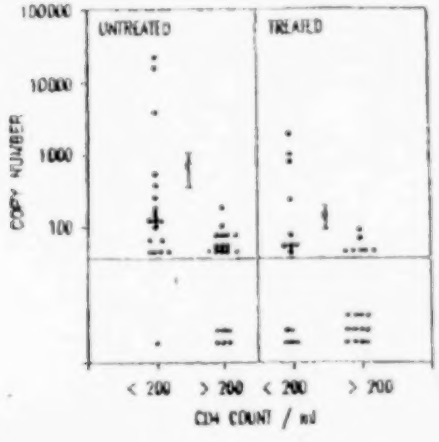
(Continued)

Primary Examiner—Bradley L. Sisson
(74) *Attorney, Agent, or Firm*—Howrey LLP

(57) **ABSTRACT**

The present invention relates to methods of monitoring, via polymerase chain reaction, the clinical progression of human immunodeficiency virus infection and its response to antiretroviral therapy. According to the invention, polymerase chain reaction assays may be used to predict immunological decline and to identify, at an early stage, patients whose infection has become resistant to a particular antiretroviral drug regimen.

8 Claims, 9 Drawing Sheets

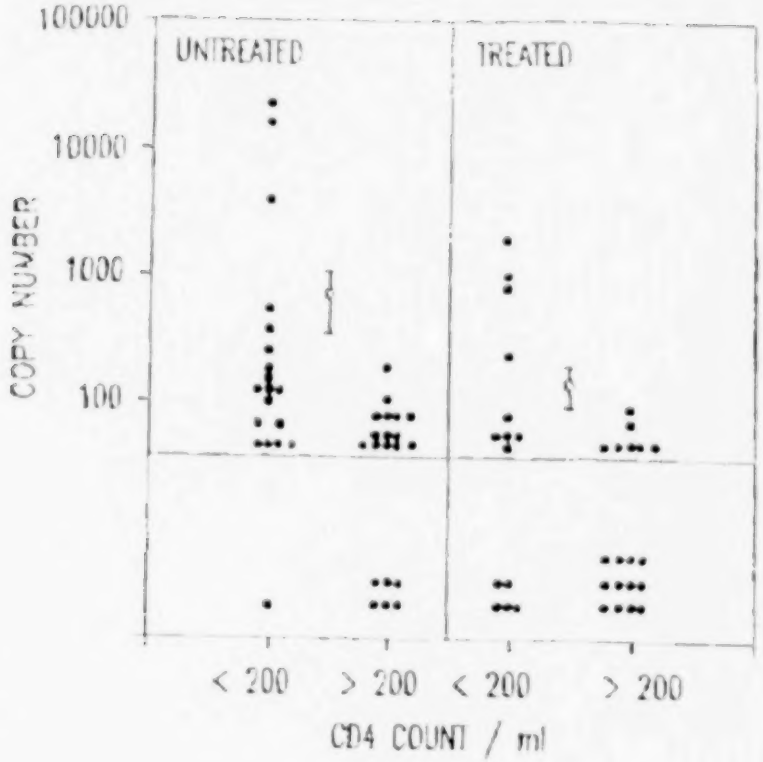


OTHER PUBLICATIONS

Defendants' Answer and Counterclaims, dated Nov. 17, 2005, as filed in the *The Board of Trustees of The Leland Stanford Junior University v. Roche Molecular Systems, Inc.*, Case No. C 05 04158 MHP, pending in the United States District Court for the Northern District of California.

Plaintiff and Counterdefendant Stanford's Reply to Counterclaims and Counterdefendant Thomas Merigan's Answer to Counterclaims, dated Dec. 21, 2005, as filed in *The Board of Trustees of The Leland Stanford Junior University v. Roche Molecular Systems, Inc.*, Case No. C 05 04158 MHP, pending in United States District Court for the Northern District of California.

* cited by examiner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CD4 COUNT / ml

FIG.1

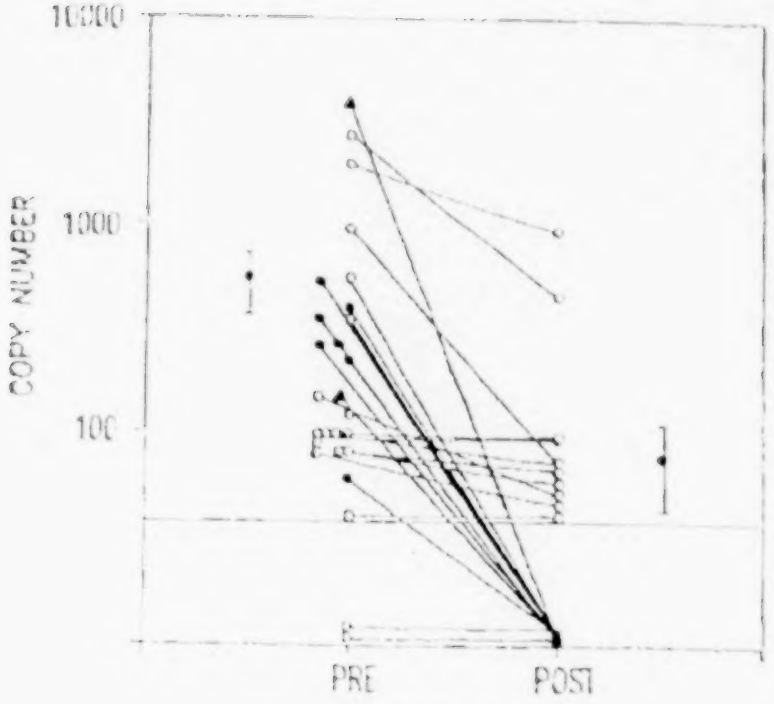
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FIG.2

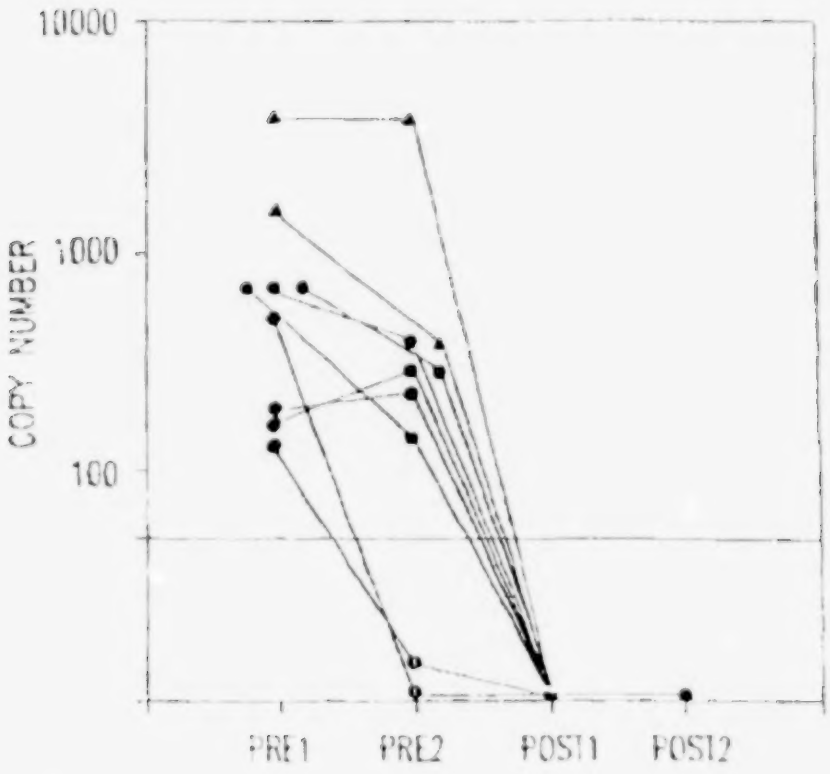
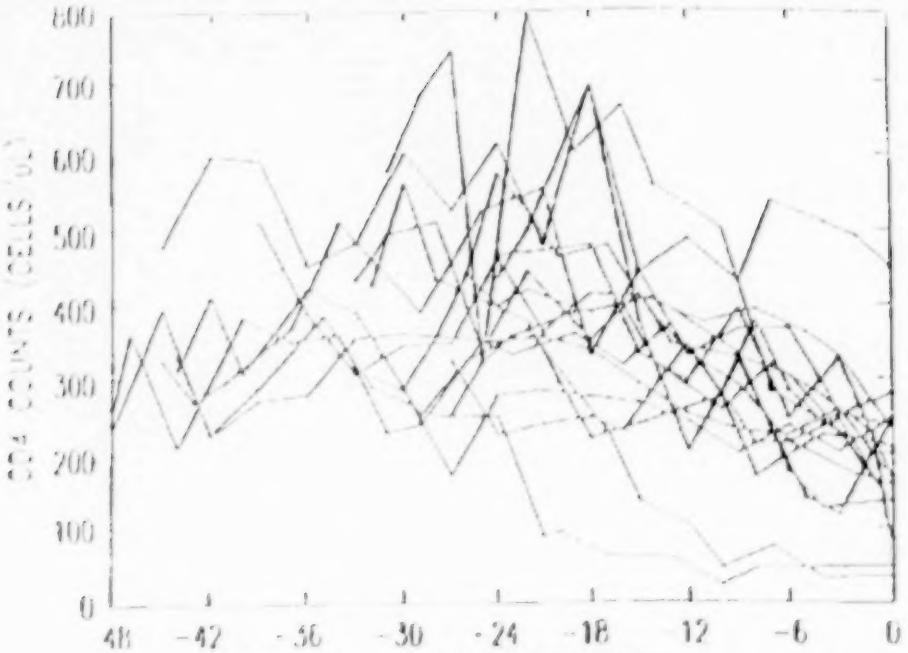


FIG.3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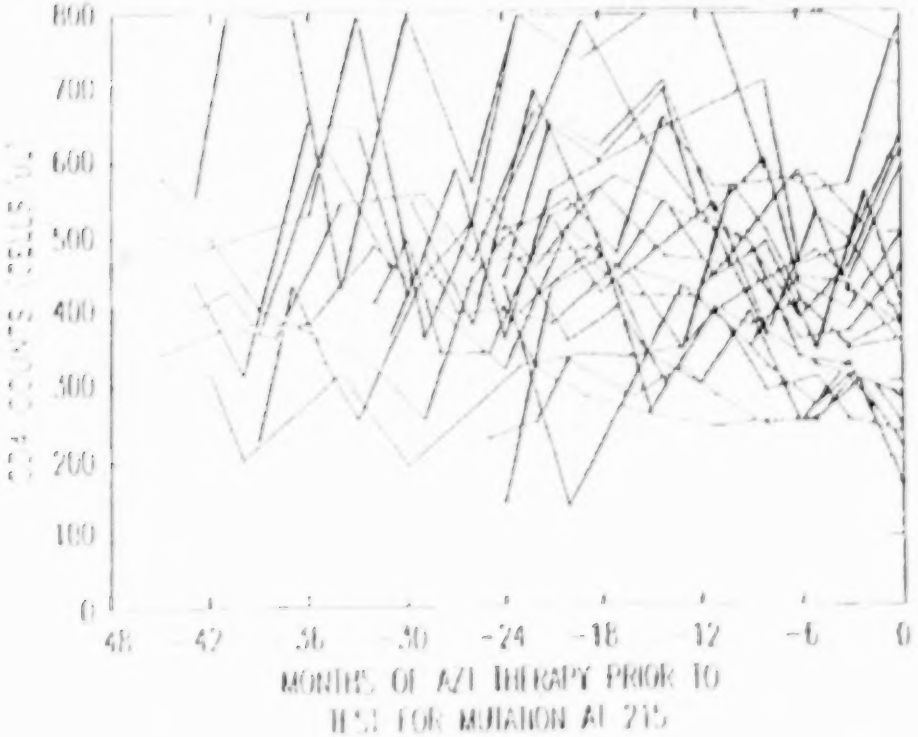
MONTHS OF A/I THERAPY PRIOR TO
TEST FOR MUTATION AT 215

FIG.4A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MONTHS OF A/I THERAPY PRIOR TO
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FIG.4B

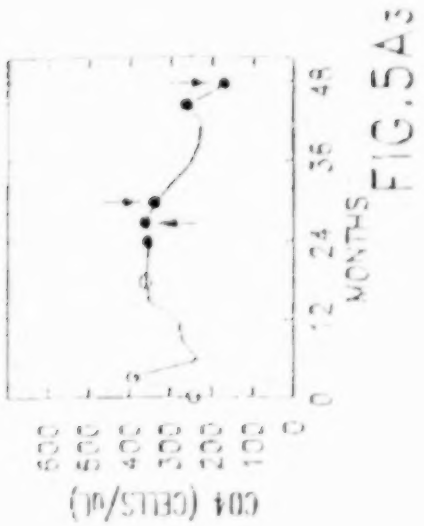

FIG.5A3

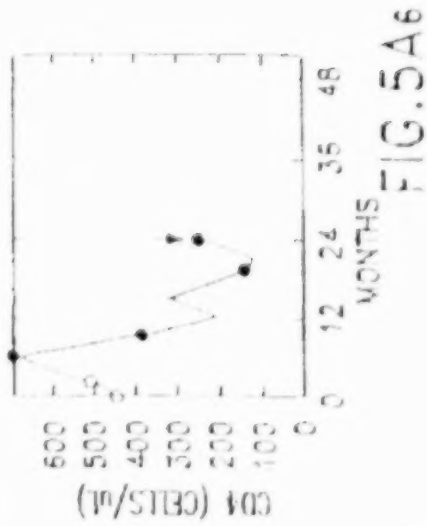

FIG.5A6

FIG.5A2

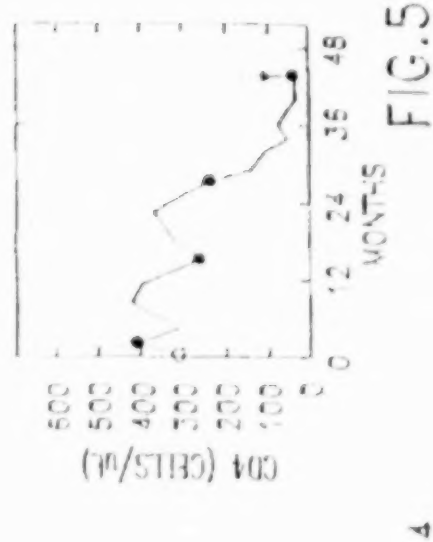

FIG.5A5

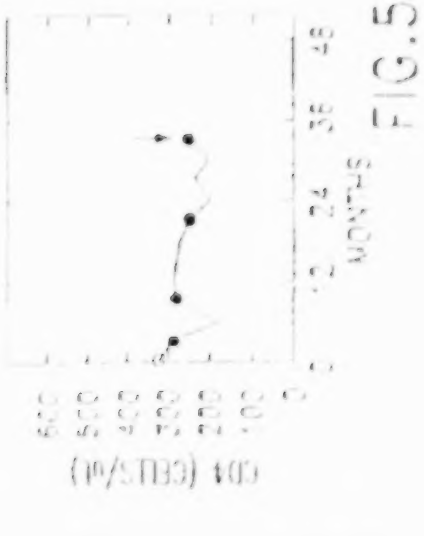

FIG.5A1

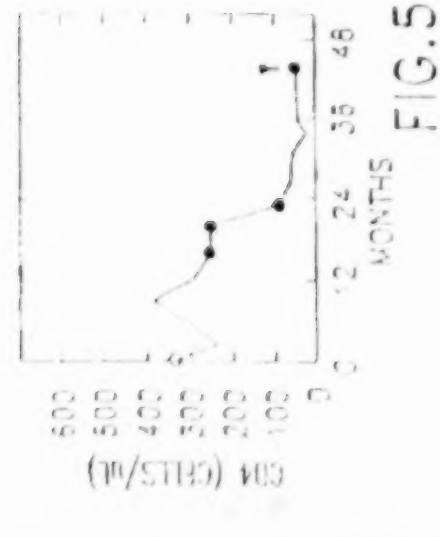

FIG.5A4

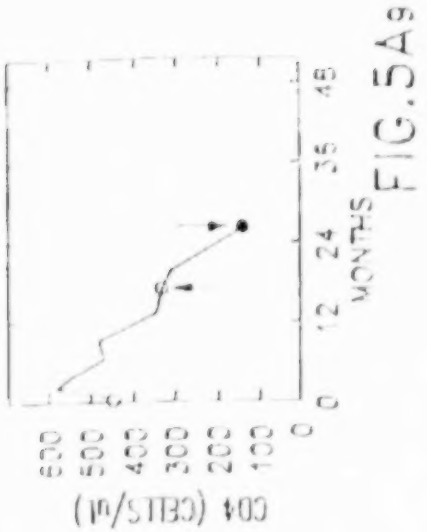

FIG.5A9

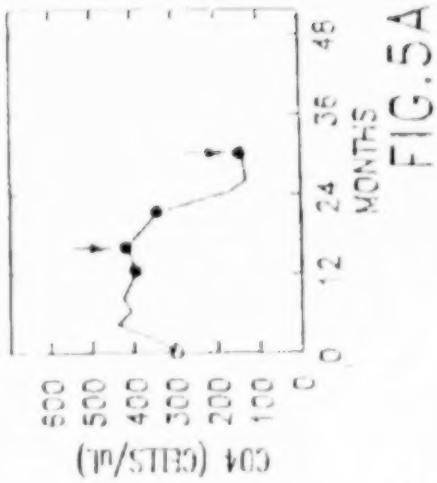

FIG.5A12

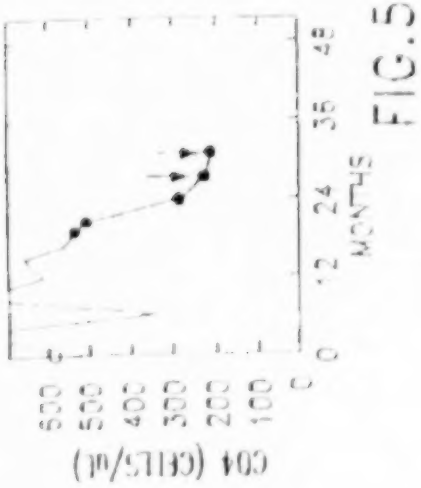

FIG.5A8

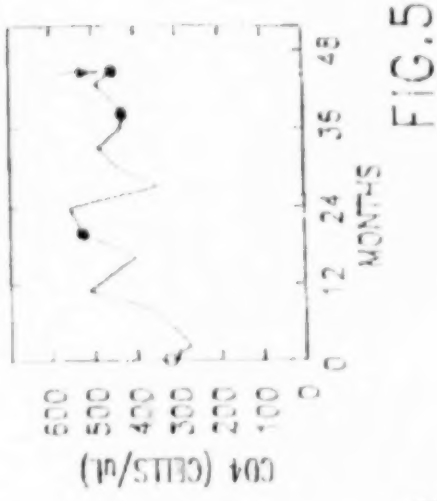

FIG.5A11

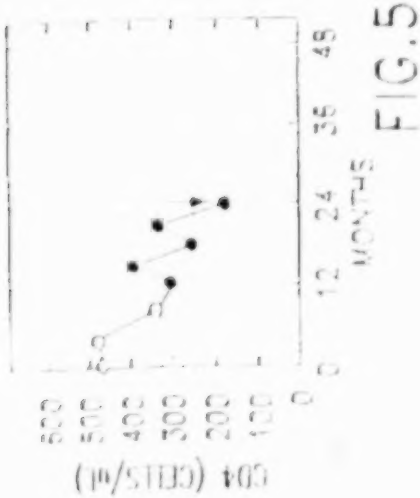

FIG.5A7

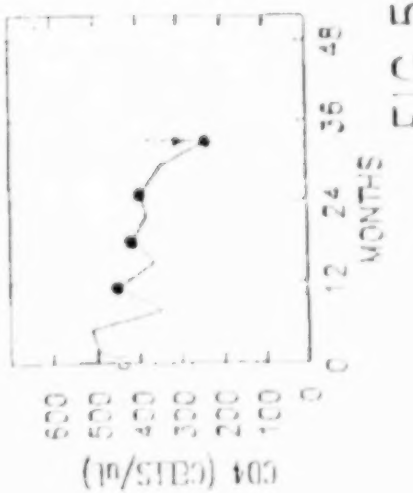

FIG.5A10

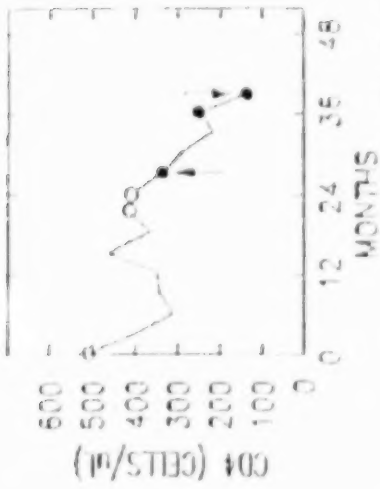

FIG.5A15

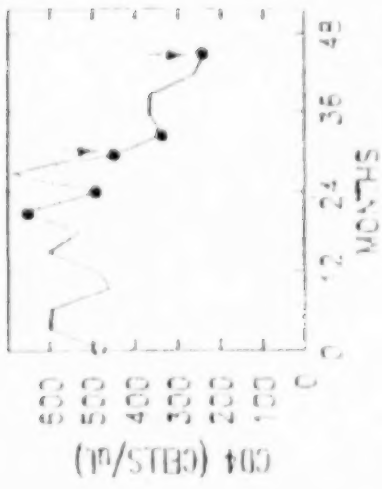

FIG.5A14

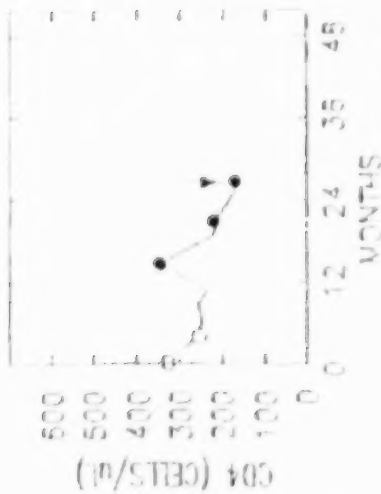

FIG.5A13

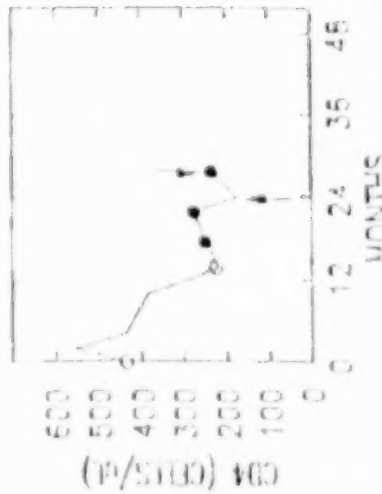

FIG.5A16

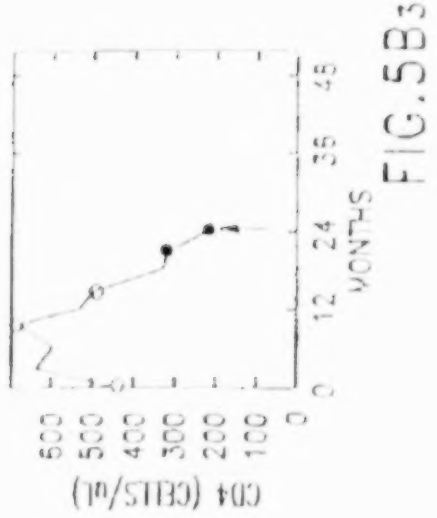

FIG.5B3

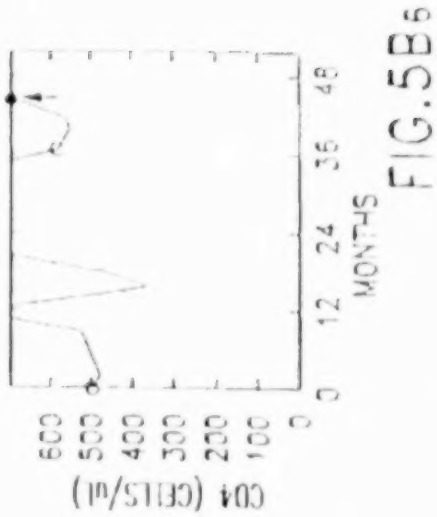

FIG.5B6

FIG.5B2

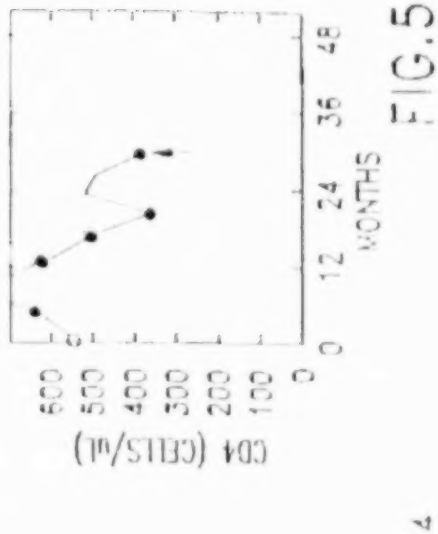

FIG.5B5

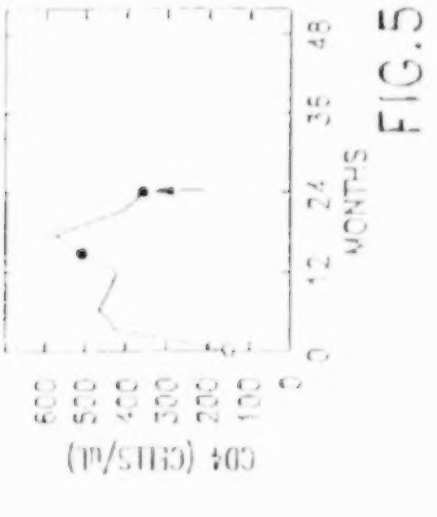

FIG.5B1

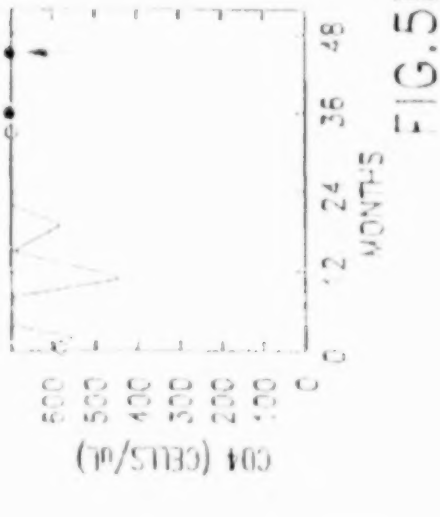

FIG.5B4

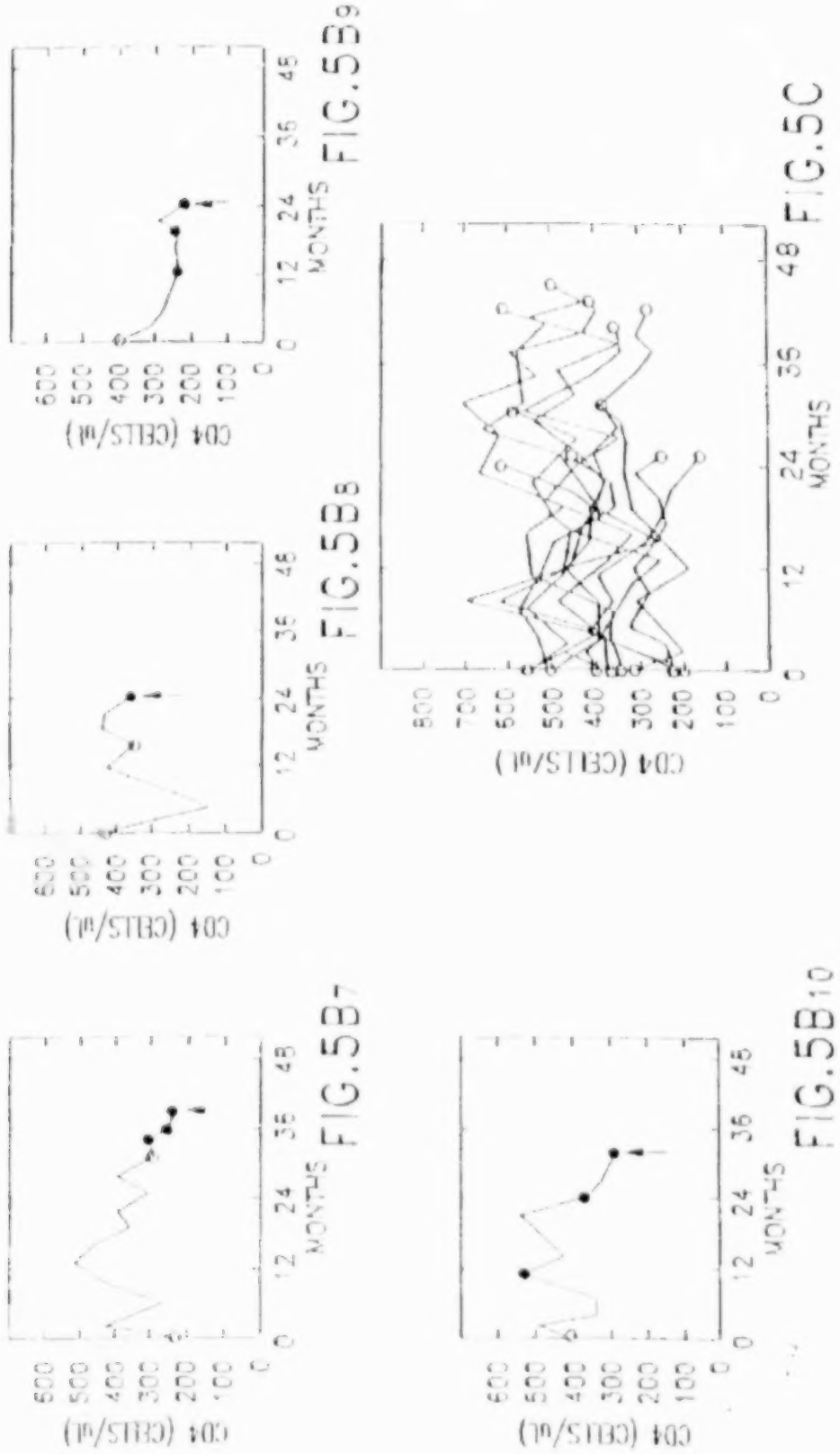
FIG.5B9
FIG.5B8
FIG.5C
FIG.5B7
FIG.5B10
CD4 (CELLS/μl)
MONTHS
0
12
24
36
48
100
200
300
400
500
600
700
800

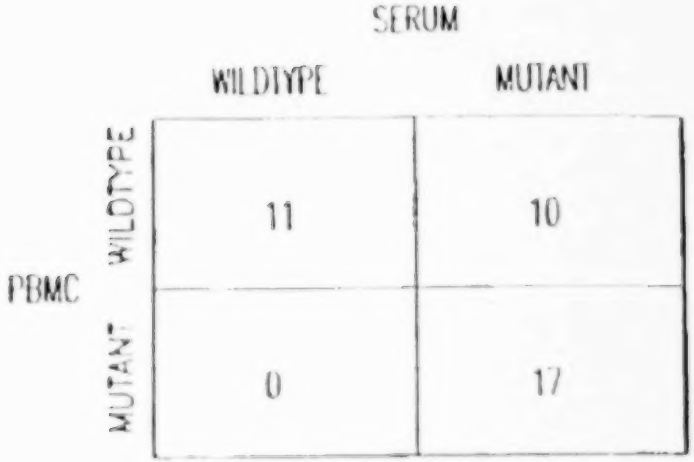

FIG.6

HIV 1
gag (p24) CORE PROTEIN

NAME OLIGO 1
SK 38 5'-ATA ATC CAC CTA TCC CAG TAG GAG AAAT

OLIGO 2
SK 39 5'-TTT GGT CCT TGT CTT ATG TCC AGA ATG C

PROBE
SK 19 5'-ATC CTG GGA TTA AAT AAA ATA GTA AGA
ATG TAT AGC CCT AC

FIG.7

POLYMERASE CHAIN REACTION ASSAYS FOR MONITORING ANTIVIRAL THERAPY AND MAKING THERAPEUTIC DECISIONS IN THE TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME

This application is a divisional application of U.S. Ser. No. 09/782,971, filed Feb. 13, 2001 now U.S. Pat. No. 6,503,705, which is a continuation application of U.S. Ser. No. 09/399,082 filed Sep. 17, 1999, abandoned, which is a continuation application of U.S. Ser. No. 08/470,885, filed Jun. 6, 1995, now U.S. Pat. No. 5,968,730, which is a divisional application of U.S. Ser. No. 07/883,327, filed May 14, 1992, abandoned. All of these applications and patents are incorporated herein by reference in their entirety. This invention was made with Government support under contracts A127762-04 and A127766-07 awarded by the National Institutes of Health. The Government has certain rights in this invention.

1. INTRODUCTION

The present invention relates to methods of monitoring, via polymerase chain reaction, the clinical progression of human immunodeficiency virus infection and its response to antiretroviral therapy. According to the invention, polymerase chain reaction assays may be used to predict immunological decline and to identify, at an early stage, patients whose infection has become resistant to a particular antiretroviral drug regimen.

2. BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) isolated from patients treated with zidovudine (AZT) may demonstrate markedly reduced in vitro susceptibility to AZT (Larder et al., 1989, Science 243:1731-1734; Rooke et al., 1989, AIDS 3:411-415; Land et al., 1990, J. Infect. Dis. 161:326-329; Boucher et al., 1990, Lancet 336:585-590; Kapour et al., 1991, Proc. Natl. Acad. Sci. 88:3092-96; Tudor-Williams et al., 1992, Lancet 339:15-19). This reduced susceptibility has been related to the duration of therapy with AZT and the severity of HIV disease at the time AZT therapy is begun (Richman et al., 1990, J. AIDS 3:743-756). Nucleotide sequence analysis of AZT-resistant HIV strains has revealed a number of mutations in the reverse transcriptase (RT) gene associated with decreased AZT susceptibility (Larder et al., 1989, Science 246:1155-1158; Larder et al., 1991, AIDS 5:137-144; Kellam et al., 1992, Proc. Natl. Acad. Sci. USA 89:1934-1938; St. Clair et al., 1991, Science 253:1557-1559; Richman et al., 1991, J. Infect. Dis. 164:1075-1081). Molecular cloning experiments have confirmed that these mutations in the RT gene confer AZT resistance (Larder et al., 1989, Science 246:1155-1158; Larder et al., 1991, AIDS 5:137-144; Kellam et al., 1992, Proc. Natl. Acad. Sci. USA 89:1934-1938; St. Clair et al., 1991, Science 253:1557-1559). Of these mutations the one at codon 215 resulting in a single amino acid substitution (Thr→Tyr or Phe) has been shown to be the most common mutation and to have the greatest impact on in vitro susceptibility to AZT (Larder et al., 1991, AIDS 5:137-144; Richman et al., 1991, J. Infect. Dis. 164:1075-1081; Boucher et al., 1992, J. Inf. Dis. 165:105-110).

Several studies have addressed the relationship between in vitro AZT resistance, mutations in the RT gene and clinical disease. Richman and coworkers studied 32 patients with different stages of HIV disease and demonstrated that the development of in vitro AZT resistance was related to the duration of therapy with AZT and to the severity of disease at the time AZT was begun (Richman et al., 1990, J.AIDS 3:743-746). Boucher and coworkers studied HIV P24-antigenemic patients treated with AZT for 2 years. They observed that at 6 months, seven patients with a mutation at codon 215 had a weak, non-statistically significant trend toward lower CD4 counts compared to nine patients who were wild type at codon 215 (Boucher et al., 1990, Lancet 336:585-590). After 2 years nearly all patents had the mutation. Tudor-Williams and coworkers studied HIV isolates from 19 symptomatic children treated with AZT for 9-39 months and showed that in vitro AZT resistance was associated with poor clinical outcome (Tudor-Williams et al., 1992, Lancet 339:15-19). However, adult studies have not shown a precise correlation between the development of in vitro resistance and progression of HIV disease.

3. SUMMARY OF THE INVENTION

The present invention relates to methods of monitoring, via polymerase chain reaction (PCR), the clinical progression of human immunodeficiency virus (HIV) infection and its response to antiviral therapy. It is based, in part, on the discovery that plasma HIV RNA copy number, as measured using PCR, may be used as a sensitive marker of the circulating HIV viral load to assess the therapeutic effect of antiretroviral compounds. In working examples described herein, an increase in plasma HIV RNA copy number was found to correlate with disease progression, and successful antiretroviral therapy was found to correlate with a decline in plasma HIV RNA copy number.

The invention is also based, in part, on the discovery that genetic changes in HIV which confer resistance to antiretroviral therapy may be rapidly determined directly from patient peripheral blood mononuclear cells (PBMC) and/or plasma HIV RNA using a "nested" PCR procedure. In working examples disclosed herein, a mutation at codon 215 of HIV reverse transcriptase (RT) was found to occur in AZT-treated patients which correlated with refractoriness to AZT treatment. The mutation was found in plasma HIV RNA one to eight months before it was detectable in PBMC. The development of the codon 215 mutation in HIV RT was found to be a harbinger of immunological decline, which occurred between six and twelve months after the mutation was detectable in plasma HIV RNA.

In particular embodiments of the invention, PCR assay may be used to monitor the clinical progression of HIV infection in patients receiving antiretroviral therapy. An increase in plasma HIV copy number detected by such an assay would correlate with refractoriness to treatment. If a patient being treated with an antiretroviral therapeutic agent exhibits an increase in plasma HIV RNA copy number, a physician should consider altering the patients treatment regimen. It should be noted that the present invention offers the advantage of being more sensitive in measuring HIV virus than standard methods which measure plasma p24 antigen or infectious virus detectable by culture techniques.

In further embodiments of the invention, PCR assay may be used to detect mutations at codon 215 of HIV RT which correlate with resistance to antiretroviral therapy and which precede immunologic decline by 6-12 months. Once mutation at codon 215 has been detected in a patient undergoing antiretroviral therapy, an alteration in the therapeutic regimen must be considered. The speed at which a modified regimen should be instituted may depend on whether the

mutation is present in plasma HIV RNA or PBMC. If the mutation is present in PBMC, a rapid alteration in therapy may be warranted.

In patients suffering from HIV infection, opportunistic infections arising as a result of a compromised immune system can be rapidly fatal. It is therefore extremely important to strive to avoid deterioration of the immune system in these patients. Because the present invention enables the early prediction of immunological decline, it allows alteration of a patient's therapeutic regimen so as to avoid opportunistic infections, and therefore may be used to promote survival and improve the quality of life of HIV-infected patients.

4. DESCRIPTION OF THE FIGURES

FIG. 1. Human immunodeficiency virus RNA copy number in 200 μl of plasma from 72 subjects as determined by cDNA gene amplification. Of 39 patients who were not currently receiving antiretroviral therapy, 20 had a CD4 count <200/mm^3 (HIV copy number 1,369±707) and 19 had a CD4 count >200/mm^3 (HIV copy number 44±10). Of 33 subjects who were currently on AZT, 14 had a CD4 count <200/mm^3 (HIV copy number 295±5) and 19 had a CD4 count >200/mm^3 (HIV copy number 16±5). Mean copy number (open circles) of subjects not on therapy was 690±360 as compared to 134±219 for patients currently on AZT ($P<0.05$, independent sample t test).

FIG. 2. Human immunodeficiency virus RNA copy number in plasma from 27 subjects before (pre) and 1 mo after (post) dideoxynucleoside therapy. (○) AZT; (●) AZT+ddI; and (▲) ddI alone. Mean copy number decreased from 540±175 to 77±35 after therapy ($P<0.05$ paired t test).

FIG. 3. Human immunodeficiency virus RNA copy number in plasma from 9 subjects with two samples obtained before initiation of therapy (pre 1 and pre 2) and two samples obtained 1 and 2 mo after commencing therapy (post 1 and post 2). (▲) ddI alone; (●) ddI+AZT.

FIG. 4. Serial CD4 counts in PBMC (cells/μl) of 17 patients in which HIV reverse transcriptase carried a mutation at codon 215 (top) and of 21 patients in which HIV reverse transcriptase was wild type at codon 215 (bottom).

FIG. 5. CD4 cell counts in PBMC from serial time points in 37 patients. ○=wild type sequence in serum specimen, ●=mutant sequence in serum. ↑=wild type sequence in PBMC, ↓=mutant sequence in PBMC; A: 16 patients mutant at codon 215 in both serum HIV RNA and PBMC (proviral DNA). B: 10 patients mutant at codon 215 in serum HIV RNA but wild type in their PBMC. C: 11 patients whom remained wild type at codon 215 in their serum HIV RNA and PBMC.

FIG. 6. Relationship of PBMC to serum genotypes in the 38 patients at study endpoint.

FIG. 7. Nucleotide sequences of SK38, SK39, and SK19 (SEQ ID NOS. 6–8).

5. DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods of monitoring, via PCR, the clinical progression of HIV infection in patients receiving antiretroviral therapy. For purposes of clarity and not by way of limitation, the detailed description of the invention is divided into the following subsections:

(i) PCR assay of plasma HIV RNA;

(ii) PCR assay of peripheral blood mononuclear cells;

(iii) PCR assay for mutation at codon 215 of HIV reverse transcriptase; and

(iv) utility of the invention.

It should be noted that heparin appears to have an inhibitory effect on gene amplification via PCR. It is therefore desireable to avoid using heparin as an anticoagulant of patient blood samples. If herapin has been used in a sample, the sample may be purified of heparin, for example, by collecting virus by ultracentrifugation.

5.1 PCR Assay of Plasma HIV RNA

According to the invention, it is desireable to avoid degradation of RNA in plasma samples prior to measurement of HIV RNA copy number. Therefore, in preferred embodiments of the invention, guanidinium is added to plasma or serum samples prior to storage at a concentration of about 2.5M and samples are kept frozen at −70° C., with no samples stored for longer than about 3 months. Serum may be used interchangeably with plasma according to the invention.

RNA may be extracted from plasma using standard techniques, such as those set forth in Chomczynski and Sacchi, 1987, Anu. Biochem. 162:156–159. For example, 200 μl of clarified plasma to which 200 μl of 5M guanidinium thiocyanate had previously been added may be extracted with phenol/chloroform and precipitated with isopropanol. The resulting pellet may then be washed in 75 percent ethanol, dried, and brought up into solution in diethylpyrocarbonate-treated glass distilled water.

From plasma RNA, WV RNA may be transcribed to cDNA using a suitable reverse transcriptase (for example, Moloney murine leukemia virus reverse transcriptase) using standard techniques, such as for example, those set forth in Kawasaki, 1990, in "PCR Protocols: A Guide to Methods and Applications," Innis et al., eds., Academic Press, Berkeley, Calif. pp. 21–27. Any suitable primer for amplification of HIV genomic RNA sequences may be used, including but not limited to, the oligomers SK38, SK39, and SK19 (FIG. 7) described in Kellog et al., 1990, in "PCR Protocols: A Guide To Methods and Applications," Innis et al., eds., Academic Press, Berkeley, Calif. pp. 337–347. In a preferred embodiment of the invention, HIV cDNA may be amplified as follows: to a 100 μreaction mixture, cDNA prepared as described supra may be added, together with 50 pmol of primers SK38 and SK39, 10 mM of each dNTP, 10 mM Tris (pH 8.3), 2.5 mM $MgCl_2$, 50mM KCl, and 2.5 U of RECOMBITAQ DNA polymerase (Perkin-Elmer Cetus, Norwalk, Conn.). The mixture may then be overlaid with 50 μl of mineral oil, and tubes containing the reaction may be placed in a DNA thermal cycler (e.g. Perkin-Elmer Cetus) for about 30 cycles of amplification with the following program: 95° C./30 seconds, 55° C./30 seconds, and 72° C./60 seconds for denaturation, annealing, and extension, respectively. Negative and positive controls which include both high and low copy number HIV RNA and DNA may be added at each step.

It is important that the number of cycles not exceed 35, and preferably, only about 30 cycles of amplification are used in the PCR. Using a greater number of cycles may detract from the sensivity of the assay.

The copy number of HIV RNA may then be measured by methods known to the skilled artisan. For example, the number of copies of HIV RNA in a patient sample may be quantitated by hybridizing the product of the above PCR with a detectably labeled probe that is complementary to HIV sequence. The amount of signal generated by probe hybrid-

ized to PCR product may then be compared to the amount of signal generated by probe hybridized to a known copy number of HIV. Probe may be detectably labeled by an enzyme, a radioisotope, a fluorescent compound, a chromogenic compound, or any other detectably labeled compound.

In a preferred, nonlimiting embodiment of the invention, at least one of the PCR primers may be biotinylated, probe may be labeled with horseradish peroxidase (HRP), and copy number may be evaluated by an enzyme-linked affinity assay as follows. 96-well microplates (Maxisorp; Nunc, Naperville, Ill.) may be coated with 100 μl of a 0.1mg/ml solution of avidin (Sigma Chemical Co., St. Louis, Mo.) in 50 mM Na_2CO_3 (pH 9.6) overnight at room temperature. Wells may then be washed twice with PBS, and then filled with 300 μl of a blocking solution containing 5xDenhardt's solution, 1% gelatin (Sigma), 250 μl/ml sheared herring sperm DNA (Promega Biotec, Madison, Wis.) at least overnight at 40° C. Immediately before use, the blocking solution may be aspirated from each well and 5 μl of PCR product prepared as described supra (using at least one biotinylated primer) may be added to each well together with 65 μl of a hybridization solution containing 5xsaline sodium phosphate EDTA, 5xDenhardt's solution, and 1 pmol of HRP-labeled SK19 HIV gag-specific probe. Because HIV primer was biotinylated, HIV amplified sequences should selectively adhere to the avidin-coated wells, so that a capture and hybridization reaction may be carried out for 1 hour at 42° C. Each well may then be washed about 20 times with PBS containing 0.05% TWEEN20™(polyoxyethylene sorbitan monolaureate), for example, using a Biomek™ 1000 Automated Workstation (Beckman Instruments, Inc., Palo Alto, Calif.). The HRP substrate O-phenylenediamine (Sigma) may then be prepared at 0.6 mg/ml in 0.1 M citrate buffer (pH 5.5) containing 0.03% hydrogen peroxide, and 150 μl of this solution may be added to each well. After about 10 minutes the reaction may be stopped with 1N H_2SO_4, and the optical density of each well measured at 490 nm, for example by the Biomek 1000. A lower level of positivity had been defined as an absorbance of 0.135. This cutoff value was calculated from the mean absorbance obtained from a group of seronegative samples plus three standard deviations. Copy number from subject samples may be determined from the absorbances obtained from a dilution series of an RNA gag gene construct of known copy number (Holodniy et al., 1991, J. Infect. Dis. 163:862-866).

In an alternate preferred, specific embodiment, RNA collected from plasma may be reverse-transcribed by using 500 ng of primer A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1) and 5 units of MuLV RT (Bethesda Research Labs) in 10 μl of amplification buffer (25 mM KCl, 50mM Tris HCl pH 8.3, 0.1 mg/ml bovine serum albumin, 1.45 mM each of dATP, dGTP, dCTP and dTTP, 1.5 mM $MgCl_2$, and 2.5 U of RNasin (Promega)) for 10 min. at room temperature, then 30 minutes at 42° C. followed by heat inactivation at 95° C. for 5 min. This cDNA may then be amplified by PCR using 250 ng of primer NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2) in a reaction mixture (100 μl) containing the same buffer as above with 0.25 mM of each dNTP and 2.5 U of AMPLITAQ DNA polymerase, using about 30 cycles of 94° C. for 1 min., 45° C. for 1 min., and 72° C. for 2 min., to generate a 768 bp region of the HIV pol gene.

5.2 PCR Assay of Peripheral Blood Mononuclear Cells

Peripheral blood mononuclear cells (PBMCs) may be used fresh or following cryopreservation (e.g. at −190° C.). DNA may be prepared from PBMCs using standard techniques for use in detection of HIV proviral DNA. Any suitable HIV primer oligonucleotide(s) may be used in PCR to detect HIV provirus.

In a preferred, nonlimiting embodiment of the invention, cryopreserved (−190° C.) PBMC may be treated with a lysis buffer (for example, 0.45 percent TWEEN-20™ (polyoxyethylene sorbitan monolaureate), 10 mM Tris HCl pH 8.0, 2.5 mM $MgCl_2$, 50 mM KCl, and 0.1 mg/ml proteinase K) for about two hours at 56° C. and then heat inactivated at 95° C. for 10 minutes. Approximately 1 μg of DNA (20 μl of the PBMC lysate) may be used in the initial PCR amplification with primers A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1) and NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2) with reaction conditions as set forth in Larder et al., 1991, AIDS 5:137-144 to generate a 768 bp region of the HIV pol gene.

5.3 PCR Assay for Mutation at Codon 215 of HIV Reverse Transcriptase

To analyse the changes in codon 215 of the HIV pol gene, a "double" or "nested" PCR procedure was performed using the primers, reagents, and reaction conditions described by Larder et al., 1991, AIDS 5:137-144. Five μl of the 768 bp product generated by PCR with primers A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1) and NE1 (5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2) and either plasma HIV RNA or PBMC DNA may be used in a second series of nested PCR amplifications using primers that detect wild-type sequence or sequence mutated at codon 215. In preferred, non-limiting embodiments of the invention, the following primers may be used: to detect wild-type sequence primers B (5'-GGATGGAAAGGATCACC-3') (SEQ ID NO:3) and 3 W (3'-TGGTGTGGTCTGTTTTTTGTA-5') (SEQ ID NO:4) and to detect mutants at codon 215, primers B (supra) and 3M (3'-AAGTGTGGTCTGTTTTTTGTA-5') (SEQ ID NO:5). PCR may then be performed as follows. About 1 μl of template may be used per PCR reaction in 100 μl containing 25 mM KCl, 50 mM Tris HCl pH 8.3, 0.1 mg/ml bovine serum albumin (BSA), 0.2 mM each of dATP, dGTP, dCTP and dTTP, 0.25 μl of each oligonucleotide primer, and 1.5 mM $MgCl_2$. Reaction mixtures may be heated at 100° C. for two minutes prior to addition of TAQ DNA polymerase (2.5 U, Perkin-Elmer Cetus, Conn.), overlaid with 100 μl of light mineral oil, and subjected to 30 cycles consisting of a denaturation step (1 minute, 94° C.), primer annealing (30 seconds, 45° C.) and DNA synthesis (30 seconds, 72° C.) using, for example, a Perkin Elmer Cetus DNA thermal cycler. Ten μl of PCR product from each set of "nested" PCR reactions may then be analyzed to determine the presence and intensity of the products. For example, PCR reactions may be analyzed on a 3.0 percent agarose gel with ethidium bromide staining; a portion of a patient sample subjected to "nested" PCR using primers B and 3W may be run in a lane next to another portion of the same patient sample subjected to "nested" PCR using primers B and 3M. A 210 bp PCR product would be expected if the patient sample contained HIV RT having the codon 215 mutation; the lane carrying primer B/3M PCR product should exhibit a band that is more intense than any corresponding band in the primer B/3W lane. If the patient sample

contained only wild type HIV RT, the band in the primer B/3W lane should be more intense than any corresponding band in the primer B/3M lane. Alternatively, if the patient sample contained a mixture of wild type and mutant HIV RT, bands of similar intensities should be in both lanes.

5.4 Utility of the Invention

The present invention relates to methods of monitoring, via PCR, the clinical progression of HIV infection in patients receiving antiretroviral therapy. Techniques described in Sections 5.1 through 5.3 supra, may be used as set forth below.

In one particular embodiment, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent; (ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and (iii) testing for the presence of HIV sequence in the product of the PCR, in which the absence of detectable HIV sequence correlates positively with the conclusion that the antiretroviral agent is therapeutically effective and the presence of detectable HIV sequence correlates positively with the conclusion that the antiretroviral agent is therapeutically ineffective. In further, related, embodiments, the presence of detectable HIV sequence correlates positively with an absolute CD4 count of less than 200 cells/mm^3, and the absence of detectable HIV sequence correlates positively with a CD4 count greater than 200 cells/mm^3. The phrase "correlates positively," as used herein, indicates that a particular result renders a particular conclusion more likely than other conclusions.

In another particular embodiment, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent; (ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and (iii) measuring the HIV RNA copy number using the product of the PCR, in which an HIV RNA copy number greater than about 500 correlates positively with the conclusion that the antiretroviral agent is therapeutically ineffective, and an HIV RNA copy number less than about 200 correlates positively with the conclusion that the antiretroviral agent is therapeutically effective.

In a further embodiment, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting one pre-treatment plasma sample from an HIV-infected patient who is about to be treated with an antiretroviral agent; (ii) collecting a post-treatment plasma sample from the HIV-infected patient after the patient has been treated with the antiretroviral agent; (iii) amplifying the HIV-encoding nucleic acid in the pre-treatment and post-treatment plasma samples using HIV primers in about 30 cycles of PCR; (iv) measuring the HIV RNA copy number using the products of the PCRs of step (iii); and (v) comparing the HIV RNA copy number in pre-treatment and post-treatment plasma samples, in which a ratio of HIV RNA copy number in pre-treatment and post-treatment plasma samples of greater than about 4 to 1 correlates positively with the conclusion that the antiretroviral agent is therapeutically effective.

In additional embodiments of the invention, PCR assay may be used to detect mutations at codon 215 of HIV RT which correlate with resistance to antiretroviral therapy and which precede immunologic decline by 6–12 months. Accordingly, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with an antiretroviral agent; and (ii) determining (for example, using "nested" PCR) whether the plasma sample comprises nucleic acid encoding HIV RT having a mutation at codon 215, in which the presence of the mutation correlates positively with immunologic decline of the patient within a six to twelve month period. Under such circumstances, the HIV virus infecting the patient has become, via the mutation, resistant to the antiretroviral agent. It therefore maybe desirable after detecting the mutation, to either increase the dosage of antiretroviral agent, change to another antiretroviral agent, or add one or more additional antiretroviral agents to the patient's therapeutic regimen. For example, if the patient was being treated with zidovudine (AZT) when the mutation arose, the patient's therapeutic regimen may desirably be altered, within about a six to twelve month period of the mutation's occurrence, by either (i) changing to a different antiretroviral agent, such as dideoxyinosine (ddI) and stopping AZT treatment; or (ii) increasing the dosage of AZT; or (iii) adding another antiretroviral agent, such as ddI, to the patient's therapeutic regimen. The effectiveness of the modification in therapy may be evaluated, as set forth above, by monitoring the HIV RNA copy number. A decrease in HIV RNA copy number correlates positively with the effectiveness of a treatment regimen.

Because the mutation at the 215 codon appears first in plasma HIV RNA and later in PBMC proviral DNA, once the mutation is detected in proviral DNA, the treatment regimen is desirably modified with haste in order to avoid immune decline. Accordingly, the present invention provides for a method of evaluating the effectiveness of antiretroviral therapy of a patient comprising (i) collecting PBMC from an HIV-infected patient who is being treated with an antiretroviral agent; and (ii) determining whether the PBMC comprise proviral HIV DNA which comprises a mutation at codon 215, in which the presence of the mutation correlates positively with immunologic decline of the patient within a 4–11 month period (because, as discussed in Section 7, infra, a mutation in serum HIV RNA was found to precede the mutation in proviral DNA by 1–8 months). Once the mutation is detected in proviral DNA, immune decline becomes even more imminent, and alteration of the patient's therapeutic regimen is desirable.

When immune decline is heralded by the increase in HIV RNA copy number and/or the presence of the mutation at codon 215, in addition to altering the patient's antiretroviral therapy, it may also be desirable to treat the patient prophylactically for opportunistic infections, using antifungal, antibiotic, and/or antiparasitic medications.

Antiretroviral agent, as used herein, includes any known antiretroviral agent including, but not limited to, dideoxynucleosides. In preferred embodiments of the invention the antiretroviral agent is AZT. Resistance to certain antiretroviral agents, including AZT, is associated with a mutation at codon 215. Resistance to other antiretroviral agents, such as ddI, is associated with a mutation at codon 74. The present invention provides for analogous techniques in which the effectiveness of antiretroviral therapy is monitored by determining whether plasma HIV RNA or PBMC contain a mutation at codon 74 of HIV RT, in which a mutation at that locus may augur immunological decline and may warrant a modification of antiretroviral therapy.

One preferred, non-limiting, specific embodiment of the invention is as follows: A method of evaluating the effectiveness of AZT therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with AZT; (ii) amplifying the HIV-encoding RNA in the plasma sample by converting the RNA to cDNA and amplifying HIV sequences using HIV primers in about 30 cycles of PCR; and (iii) testing for the presence of HIV sequence in the product of the PCR, in which the absence of detectable HIV sequence correlates positively with the conclusion that AZT is therapeutically effective and the presence of detectable HIV sequence correlates positively with the conclusion that AZT is therapeutically ineffective. In most preferred embodiments, the HIV primers used comprise NE1 (supra), SK38 and/or SK39 (supra), and/or the presence of HIV sequence is detected using an enzyme-linked assay (e.g., a horseradish peroxidase based assay). Similar embodiments in which the HIV copy number is measured are also provided for.

Another preferred, non-limiting, specific embodiment of the invention is as follows: A method of evaluating the effectiveness of AZT therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with AZT; (ii) amplifying the HIV-encoding RNA in the plasma sample by converting the RNA to cDNA and amplifying HIV sequences using HIV primers that result in a PCR product that comprises that portion of the RT gene that contains the 215 codon (e.g. primer NE1, supra); (iii) performing "nested" PCR using primers that result in PCR products that reflect the presence of wild type (e.g. primers B and 3W, supra) or 215 codon mutant (e.g. primers B and 3M, supra); and (iv) determining, via the products of "nested" PCR, the presence or absence of a mutation at codon 215 of the HIV RT, in which the presence of the mutation correlates positively with immunologic decline of the patient within a six to twelve month period. An analogous method may be used in which the patient sample is PBMC, and the presence of a mutation is proviral DNA is determined.

6. EXAMPLE

Reduction in Plasma Human Immunodeficiency Virus Ribonucleic Acid After Dideoxynucleoside Therapy as Determined by the Polymerase Chain Reaction

6.1 Materials and Methods

6.1.1 Patients

After informed consent was obtained, whole blood samples were collected by venipuncture in the presence of acid-citrate-dextrose as an anticoagulant. A single plasma sample was collected from 39 HIV antibody-positive subjects who were not receiving antiretroviral therapy at the time of collection and from 33 HIV antibody-positive subjects who were currently on and had received AZT for a minimum of 3 mo.

Two plasma samples were collected from an additional 27 subjects before and 1 month after initiation of dideoxynucleoside therapy. 18 of these subjects received 500 mg/d of AZT orally. Seven subjects received a combination of zidovudine (150–600 mg/d) and 2',3'-dideoxyinosine (ddI) (134–500 mg/d). Two patients received 500 mg/d of ddI alone (see Table 1 for individual subject characteristics). Finally, nine of these subjects had two plasma samples taken 1–3 wk before initiating antiretroviral therapy and two plasma samples taken 1 and 2 mo after commencing therapy. Plasma was separated within 4 h by centrifugation at 800 g for 10 min. A second centrifugation was performed on the plasma at 800 g for 30 min to remove any cellular material. 200 μl of plasma was then mixed with 200 μl of a solution containing 5 M guanidinium thiocyanate, vortexed briefly, and stored at −70° C. until further use. All samples were assayed within 3 mo of collection. To decrease variance, all specimens to be compared from the same subject were run in the same assay.

6.1.2 Extraction of RNA from Plasma

RNA was extracted from plasma by the method described in Chomczynski et al., 1987, Ann. Biochem. 162:156–159. Briefly, 200 μl of clarified plasma to which 200 μl of 5 M guanidinium thiocyanate had previously been added was extracted with phenol/chloroform and precipitated with isopropanol. The resulting pellet was then washed in 75% ethanol, dried, and brought up in diethylpyrocarbonate treated, glass distilled water.

6.1.3 Reverse Transcription and Amplification of cDNA

HIV RNA was transcribed to cDNA using Moloney murine leukemia virus reverse transcriptase (Bethesda Research Laboratories, Gaithersburg, Md.) by the method described in Kawasaki, 1990, "In PCR Protocols: A Guide to Methods and Applications" pp. 21–27, M. A. Innis, D. H. Gelfand, J. J. Sninsky, and T. J. White, eds. Academic Press, Berkeley, Calif. Oligomers used for amplification included SK38, SK39, and SK19 (Kellog et al., 1990, "In PCR Protocols: A Guide to Methods and Applications," pp. 337–348, M. A. Innis, D. H. Gelfand, J. J. Sninsky, and T. J. White, eds. Academic Press, Berkeley, Calif.). Biotinylation of SK38 and horseradish peroxidase (HRP) labeling of probe SK19 were prepared as described in Levenson et al., 1990, "In PCR Protocols: A Guide to Methods and Applications," pp. 99–112 M. S. Innis, D. H. Gelfand, J. J. Sninsky, and T. J. White, eds. Academic Press, Berkeley, Calif. Amplification of HIV cDNA was carried out as follows: to a 100-μA reaction mixture was added the cDNA, 50 pmol of primers SK38 and SDK39, 10 mM of each dNTP, 10 mM Tris (pH 8.3), 2.5 mM $MgCl_2$, 50 mM KCl, and 2.5 U of RECOMBITAQ DNA polymerase (Perkin-Elmer Cetus, Norwalk, Conn.). The mixture was then overlaid with 50 μl of mineral oil. Tubes were placed in a DNA thermal cycler (Perkin-Elmer Cetus) for 30 cycles of amplification with the following program: 95° C./30 s, 55° C./30 s, and 72° C./60 s for denaturation, annealing, and extension, respectively. Negative and positive controls which included both high and low copy number WV RNA and DNA were added at each step.

6.1.4 Enzyme-Linked Affinity Assay

To detect and quantitate PCR product, 96 well microplates (Maxisorp, Nunc, Naperville, Ill.) were coated with 100 μl of a 0.1 mg/ml solution of avidin (Sigma Chemical Co., St. Louis, Mo.) in 50 mM Na_2CO_3 (pH 9.6) overnight at room temperature. Wells were then washed twice with PBS. Wells were then filled with 300 μl of a blocking solution containing 5×Denhardt's solution, 1% gelatin (Sigma), 250 μl/ml sheared herring sperm DNA (Promega Biotec, Madison, Wis.) at least overnight at 4° C. Immediately before use, the blocking solution was aspirated from each well and 5 μl PCR product and 65 μl of a hybridization solution, containing 5×sodium sodium phosphate/EDTA, 5×Denhardt's solution, and 1 pmol of HRP labeled SK19 HIV gag specific probe was added to each well. A capture

and hybridization reaction was then carried out in the well for 1 h at 42° C. The 96-well microplate was then placed in a Biomek™ 100 Automated Workstation (Beckman Instruments, Inc., Palo Alto, Calif.) where wells were washed 20 times with BPS containing 0.05% TWEEN-20™ (polyoxyethylene sorbitan monolaureate). The HRP substrate O-phenylenediamine (Sigma) was prepared at 0.6 mg/ml in 0.1 M citrate buffer (pH 5.5) containing 0.03% hydrogen peroxide. 150 μl of this substrate solution was added to each well. After 10 min the reaction was stopped with 1 NH_2SO_4 and the optical density of each well measured at 490 nm by the Biomek 1000. A lower level of positivity had been defined as an absorbance of 0.135. This cutoff value was calculated from the mean absorbance obtained from a group of seronegative samples plus three standard deviations. Copy number from subject samples were determined from the absorbances obtained from a dilution series of an RNA gag gene construct of known copy number described in Holodniy et al., 1991, J. Infect. Dis. 163:862–866. The lower level of sensitivity in this assay was 40 copies of HIV gag gene RNA.

6.1.5 Plasma HIV Culture and P24 Antigen Assay

Quantitative HIV plasma microculture was performed according to the method described in Ho et al., 1989, N. Engl. J. Med. 321:1621–1625. P24 antigen was detected by an antigen capture assay by a method provided by the supplier (Abbott Laboratories, North Chicago, Ill.).

6.1.6 Statistical Analysis

Sample optical density was converted to copy number and analyses performed on samples expressed as RNA copy number/200 μl of plasma. A t test of independent samples was used in analysis of subject who did not receive antiretroviral therapy compared to subjects who were receiving AZT. A t test of paired samples was used to analyze paired plasma data and CD4 counts from subjects pre- and post therapy. All t tests were two tailed. A Fisher's exact test or chi square test were used for analysis of proportion where appropriate. Statistical significance was defined as $P<0.05$.

6.2 Results

72 subjects were evaluated in a cross sectional study of HIV disease to determine plasma HIV RNA copy number by PCR. The results are presented in FIG. 1. 39 subjects who were not currently receiving antiretroviral therapy and 33 subjects who were receiving AZT were evaluated. Untreated subjects were more likely to have a positive signal than treated subjects (32 of 39 vs. 16 of 33, respectively, P 0.008, chi square). In the 39 subjects who were not currently receiving therapy, the mean plasma HIV RNA copy number was 690±360 (mean±SEM) per 200 μl of plasma, while the 33 subjects who had been receiving AZT therapy had a mean copy number of 134±219 ($P<0.05$). Mean CD4 count for each group was 316±45 and 300±37, respectively (P=NS).

Subgroups were then analyzed with respect to CD4 count. Among those with <200 CD4 cells, untreated subjects were more likely to have positive signal than treated subjects (18 of 19 vs. 9 of 14, $P<0.04$, Fisher's exact test). Among those with >200 CD4 cells, 14 of 20 untreated subjects vs. 7 of 18 treated subjects had a detectable signal (P=NS, Fisher's exact test). Untreated subjects with CD4 count <200/mm³ had a mean RNA copy number of 1,369±707 and mean CD4 count of 73±17; untreated subjects with CD4>200/mm³ had a mean RNA copy number of 44±10 and mean CD4 count of 547±45; treated subjects with CD4 counts <200/mm³ had a mean RNA copy number of 295±5 and mean CD4 count of 115±13; and treated subjects with CD4 counts >200/mm³ had calculated mean RNA copy number of 16±5 (which is below the level of detection of this assay and would be interpreted as negative) and mean CD4 count of 437±41.

27 additional subjects were then evaluated before and 1 mo after initiation of dideoxynucleoside therapy. Clinical parameters of the subjects are presented in Table 1. PCR results are presented in FIG. 2. Results show that plasma HIV RNA copy number fell from 540±175 to 77±35 after therapy ($P<0.05$, paired t test). Mean CD4 count increased from 399±24 to 442±25 after 4 wk of therapy ($P<0.006$, paired t test).

TABLE 1

Clinical Parameters and PCR Analysis of Plasma HIV RNA from 27 Patients

Patient No.	Antiviral treatment	Pretreat CD4	Pretreat HIV RNA
1*	AZT‖	84/561	168/90
2*	AZT	54/65	1360
3	AZT	840/834	5960
4	AZT	432/462	10077
5*	AZT	318/415	8757
6*	AZT	478/408	4042
7	AZT	452/345	9696
8	AZT	430/402	0/0
9	AZT	432/532	9765
10	AZT	430/430	10585
11	AZT	439/404	12650
12	ddI + AZT§	280/220	5260
13	AZT	323/320	7845
14	AZT	320/458	9595
15	AZT	353/387	3010
16	ddI + AZT§	309/399	3000
17	ddI + AZT§	337/398	2660
18	ddI‖	328/310	9660
19	ddI+ AZT¶	383/491	2450
20	AZT	404/433	0/0
21	AZT	270/450	9587/2
22	ddI + AZT¶	295/344	0/0
23	AZT	320/295	27864/3
24	ddI‖	222/370	9944/0
25	AZT	568/732	20149/25
26	DDI + AZT**	387/473	2170
27	DDI + AZT**	310/369	4360

*Remote history of AZT use.
†AZT dose 300 mg/d unless otherwise stated.
§AZT 300 mg/d + ddI 334 mg/d.
‖ddI 500 mg/d.
¶AZT 300 mg/d + ddI 500 mg/d.
**AZT 150 mg/d + ddI 134 mg/d.

Finally, 9 of the 27 subjects had two samples taken before initiation of therapy and two samples taken 1 and 2 months after commencing therapy. The results are presented in FIG. 3. When two pretherapy time points were analyzed for constancy of signal, results show that mean copy number for each pretherapy time point was 945±377 and 643±392.

Two subjects had a second pretherapy sample which was negative. When both pretherapy copy number values were compared to posttherapy values, plasma HIV RNA copy number fell from 794±274 to <40 (which is below the lower level of detection in this assay) after 1 and 2 mo of therapy ($P<0.05$, paired t test). Mean CD4 count increased from 314±165 to 378±25 ($P<0.05$, paired t test).

Plasma culture was performed on fresh material obtained from the initial pretreatment sample for 23 of 27 of these patients. Only 7 of 23 were plasma virus positive by culture (from 1 to 100 tissue culture infective dose/ml). All 23 of these patients were positive by PCR (>40 copies/200 μl). In

addition, a p24 antigen test was performed on all 27 pretreatment samples. Only 2 of 27 had detectable p24 antigen present (>30 pg/ml).

6.3 Discussion

The results presented here demonstrate that plasma HIV RNA can be detected and quantified by copy number in the majority of patients infected with HIV. In addition, plasma HIV RNA copy number may be used as a marker of circulating HIV viral load to assess treatment effect of antiretroviral compounds including dideoxynucleoside compounds. We initially conducted a survey to determine whether treatment or degree of immunologic impairment, based on CD4 count, affected plasma HIV RNA copy number. Untreated patients as a group had higher copy numbers than treated patients. Untreated patients with <200 CD4 cells/mm^3 had a higher mean copy number than patients with >200 CD4 cells/mm^3. Likewise, treated patients with <200 CD4 cells/mm^3 had higher copy numbers than patients with >200 CD4 cells/mm^3, indicating that patients with more advanced HIV disease have higher circulating copy numbers than asymptomatic patients, and that the antiretroviral benefit seen in patients with higher CD4 counts may be waning.

To assess the short-term impact of antiretroviral therapy on patients, 27 patients were evaluated before and 1 mo after initiation of A/T, ddI, or combination therapy. As CD4 counts increased after 1 mo of therapy, HIV RNA copy number fell significantly. However, the response of individual subjects was variable. 16 of 27 subjects had a marked decrease in copy number and 11 of 27 did not. Because the majority of subjects received A/T alone, it was not possible to assess any differences between A/T, ddI, or combination regimens.

Finally, nine subjects had two baseline time points taken in the 3 wk before treatment, followed by two monthly samples posttreatment. Pretreatment signal was constant in 7 of 9 subjects, and 2 subjects had discordant samples, i.e., one was positive and one was negative. This could be related to real changes in circulating HIV RNA, or introduced during sample collection, handling, or the assay. However, pretherapy and posttherapy samples were run in the same assay and so were subject to all of the same reaction conditions. When sample positivity was considered in relation to therapy, 16 of 18 pretherapy samples had a positive signal vs. 0 of 18 posttherapy samples ($P<0.001$, chi square) showing suppression of HIV RNA copy number with treatment.

Currently there is no standard method to assess circulating viral load in all HIV-infected patients. Plasma viremia, measured by quantitative microculture, can identify and quantify infectious virus in 50–100% of patients, principally those with advanced stages of HIV disease, low CD4 counts, and p24 antigenemia (Ho et al., 1989, N. Engl. J. Med. 321:1621–1625; Coombs et al., 1989, J. Virol. Methods 26:23–2; Ehrnst et al., 1988, N. Engl. J. Med. 324:961–964). Many patients with >200 CD4 cells/mm^3 do not have detectible infectious plasma viremia. This may be due to an absence of circulating infectious virus, virus which is neutralized by specific antibody, or the insensitivity of culture techniques. The results presented here indicate that the majority of patients with >200 CD4 cells/mm^3 do not have plasma p24 antigen or infectious virus detectable by culture techniques. In the studies described herein, it appears that virus undetectable by culture methods was detectable by PCR methods.

Attempts have been made to assess HIV viral load in patients by molecular techniques, mainly by quantitative PCR of HIV proviral DNA in circulating mononuclear cells or cell-free virion-associated RNA in plasma. Published data suggest that the number of cells infected with HIV increases with advancing disease and that HIV proviral DNA content increases as well. We and others have shown a decrease in HIV proviral DNA with dideoxynucleoside therapy over time (Aoki et al., 1990, AIDS Res. Hum. Retroviruses 6:1331–1339). This was not the case in another published small series (McElrath et al., 1991, J. Clin. Invest. 87:27–30).

We have shown that HIV RNA could be quantified in serum and that copy number increased with disease progression (Holodniy et al., 1991, J. Infect. Dis. 163:862–866). Plasma HIV RNA has been shown to be present before and after seroconversion with quantitative decreases occurring after seroconversion (Hewlett et al., 1988, J. Clin. Immunoassay 11:161–164). The recent report by Daar et al. (Daar et al., 1991, N. Engl. J. Med. 324:961–964), showed a decrease in both plasma viremia and proviral DNA from PBMC, coinciding with seroconversion after acute infection. In one report, plasma HIV RNA levels fell with passive immunoglobulin therapy, suggesting a therapy-based response in circulating HIV RNA load (Karpas et al., 1990, Proc. Natl. Acad. Sci. USA 87:7613–7617). Ohman and colleagues have been successful in detecting HIV RNA in plasma from 95% of patients evaluated (Ohman et al., 1991, J. Virol. Methods 31:273–284). They also studied a group of patients who were receiving A/T to determine whether there was any therapeutic impact on HIV RNA signal. 24 of 25 patients who were receiving A/T had detectible signal. However, methodological differences in that study vs. the present study may have contributed to the differences noted between them. First, Ohman et al. used an ultracentrifugation step to sediment virus, enhancing virion-associated RNA recovery. Second, 40 cycles of amplification after reverse transcription were performed, which would certainly increase the sensitivity of such an assay to successfully detect HIV RNA in virtually all patients. Although sensitivity is increased with increased cycle number, thus detecting signal in virtually all patients, the ability to show the quantitative changes demonstrated here with 30 cycles of amplification is lost.

We have previously shown in serum that quantitative serum cultures were negative in the majority of patients with >200 CD4 cells/mm^3 (Holodniy et al. 1991, J. Infect. Dis. 163:862–866). In the current study, 23 plasma samples were evaluated by culture and PCR. All had detectable plasma HIV RNA by PCR but only seven were plasma HIV-culture positive. Other published experience comparing plasma HIV culture and PCR of HIV RNA from plasma is lacking. Ohman et al. tested only two patients, both of whom were positive in both assays. Coyle et al. reported that 14 of 20 patients had positive plasma cultures and 12 of 20 patients had detectable HIV RNA in plasma, but no information was given regarding concordance or discordance of samples (Coyle et al., 1990, Clin. Res. 38:778a (Abst.)).

The type of plasma sample and method of processing and storage were found to be very important. The type of anticoagulant used for sample collection can affect detection of plasma RNA. We have previously shown that plasma collected in the present of heparin does not allow detection of signal because of an inhibitory effect of heparin on gene amplification (Holodniy et al., 1991, J. Clin. Microbiol. 29:676–679). Although Coyle et al. (1990, Clin. Res. 38:778a (Abst.)) found detectable signal from plasma col-

lected in the presence of heparin, an ultracentrifugation step preceding RNA analysis lead to removal of most of the heparin from the enzyme-mediated assay system. However, no comparison experiments among anticoagulants were performed to demonstrate any attenuation of signal obtained in the presence of heparin.

Because of our concern for RNA degradation during specimen storage and freeze thawing, we decided to store fresh plasma at −70° C. in the presence of guanidinium and process samples within 3 mo of collection. Samples were stored in guanidinium for RNAase inhibition. Preliminary data from our laboratory would suggest that plasma HIV RNA signal decays with time in the absence of this RNA stabilizer.

In summary, we have shown that plasma HIV RNA copy number can be quantitated by PCR and does decrease with dideoxynucleoside therapy. The nonisotopic, microplate-based format presented here makes it possible to process multiple patient samples with replicates in a single amplification and assay run.

7. EXAMPLE

Relationship of a Mutation in the HIV Reverse Transcriptase Gene to Decline in CD4 Lymphocyte Numbers in Long Term AZT Recipients

7.1 Materials and Methods

7.1.1 Study Population

Cryopreserved PBMC and serum from 40 participants in AIDS Clinical Trial Group (ACTG) protocols 019 (30 patients) and 016 (10 patients) at Stanford University Medical Center AIDS Clinical Trial Unit were used in this study. Patients at enrollment in these studies were AZT naive, had >200 CD4 cells/μl and had few (016) or no symptoms (019) referable to HIV infection. They were subsequently treated with AZT for 2 to 4 years. The most common dosage was 500 mg per day. Approximately one third of patients received either 1200 mg or 1500 mg per day during the initial part of their therapy, but were changed to 500 mg per day when lower doses were found to be as effective but less toxic than higher doses (Fischl et al., 1990, N. Engl. J. Med. 323:1009-1014; Volberding et al., 1990, N Engl. J. Med. 322:941-949). All samples were obtained from the patients while they were on the protocols and thus no patient developed an AIDS defining diagnosis.

7.1.2 CD4 Cell Counts

CD4 cell counts were obtained approximately every three months on each patient. All counts were performed at Stanford's ACTG-qualified cytofluorometry lab. Samples were stained with monoclonal antibodies to CD3, CD4, and CD8. The absolute CD4 count was calculated by multiplying the percent CD4 by the total lymphocyte count.

7.1.3 PBMC Preparation

Cryopreserved (−190° C.) PBMC were treated with a lysis buffer (0.45% TWEEN-20™ (polyoxyethylene sorbitan monolaureate), 10 mM Tris HCl pH 8.0, 2.5 mM $MgCl_2$, 50 mM KCl, and 0.1 mg/ml proteinase K) for 2 hours at 56° C. and then heat inactivated at 95° C. for 10 min. Approximately 1 μg of DNA (20 μl of the PBMC lysate) was used in the initial PCR amplification with primers A(5'-TTCCCATTAGTCCTATT-3') (SEQ IDNO:1) and NE1(5'-TCATTGACAGTCCAGCT-3') (SEQ ID NO:2) with reaction conditions as described in Larder et al., 1991, AIDS 5:137-144 to generate a 768 bp region of the HIV pol gene.

7.1.4 Serum HIV RNA Preparation

Cryopreserved (−70° C.) serum was thawed and then 350 μl of sera was added to 350 μl of solution D (Chomczynski et al., 1987, Anal. Biochem. 162:156-159) (guanadinium thiocyanate +2-mercaptoethanol) and vortexed. RNA was then extracted with phenol and chloroform and precipitated with ethanol as described in Chomczynski et al., 1987, Anal. Biochem. 162:156-15918. HIV RNA was then reverse transcribed to cDNA by using 500 ng of primer A and 5 units of murine leukemia virus (MuLV) reverse transcriptase (Bethesda Research Labs) in 10μl of amplification buffer (25 mmol/L KCl, 50 mmol/L Tris HCl Ph 8.3, 0.1 mg/ml bovine serum albumin, 1.45 mmol/L each of dATP, dGTP, dCTP and dTTP, 1.5 mmol/L $MgCl_2$, 2.5 units of RNasin (Promega)) for 10 mm at room temperature, then 30 mm at 42° C. followed by heat inactivation at 95° C. for 5 mm. This cDNA was then amplified by PCR using 250 ng of primer NE1 in a reaction mixture (100 μl) containing the same buffer as above with 0.25 mmol/L of each dNTP and 2.5 units of AMPLITAQ DNA polymerase (Perkin-Elmer Cetus). This reaction mixture underwent 30 cycles of 94° C. for 1 mm, 45° C. for 1 mm and 72° C. for 2 min to generate a 768bp region of the HIV pol gene.

7.1.5 PCR Analysis of HIV Reverse Transcriptase Gene

To analyze the changes in codon 215 of the HIV pol gene, a "double" PCR procedure was performed using the primers, reagents, and reaction conditions described in Larder et al., 1991, AIDS 5:137-144. Five μl of the 768 bp product generated by PCR with primers A and NE1 was used in a second series of nested PCR amplifications using primer B and 3W to determine if a wild type sequence was present, or B and 3M to determine if a mutant sequence was present (primer sequences as set forth supra and in Larder et al., 1991, AIDS 5:137-144). Samples were run with negative, positive and reaction mixture controls. Ten μl of PCR product from each of the second set of PCR reactions were analyzed on a 3.0% agarose gel with ethidium bromide staining. PCR products were considered to have a mutant or wild type sequence by the method described by Boucher et al. (1990, Lancet 336:585-590; 1992, J. Infect. Dis. 165: 105-110) and Larder et al., 1991, AIDS 5:137-144: a sample was considered to contain the wild type sequence at codon 215 if amplification with the primers B and 3W resulted in a 210 bp PCR product of highest intensity; a sample was considered to contain a mutant sequence at codon 215 if amplification with the primers B and 3M resulted in a 210 bp PCR product of highest intensity. The sample was considered to have a mixture of wild type and mutant sequences if amplification occurred with both primers 3M and 3W resulting in PCR products of similar intensity. If a mixture was detected by PCR then that sample was included in the mutant group in our statistical analysis.

7.1.6 AZT Sensitivity Assay

Patient PBMC were cocultured with mitogen-stimulated PBMC from healthy HIV-seronegative donors. Supernatants from these cultures were collected and frozen when the HIV P24 antigen concentration exceeded 10,000 pg/ml. 30-100 $TCID_{50}$ (50% tissue culture infectious dose) of virus stock was used to infect one million donor PBMC pretreated with different concentrations of AZT (0.0 uM, 0.005 uM, 0.05 uM, 0.5 uM, 5.0 uM). After 7 days, P24 antigen was measured in the cell free supernatant from the cultures with and without zidovudine. The concentration of AZT required

to inhibit P24 production by 90% (IC_{90}) as compared to the drug free cultures was determined by nonlinear regression analysis (Chou et al., 1984, Adv. Enzyme Regulation 22:27-55). In this assay, the IC_{90}s from AZT-naive patients ranged from 0.002 μM to 0.038 μM AZT.

7.1.7 Statistical Analysis

All comparisons between the patients with mutant and wild type strains were performed using the student's t-test. The calculations on the IC_{90}s determined by the zidovudine sensitivity assay were performed using the $\log_{10}$ transformed IC_{90} (i.e. geometric means were used rather than arithmetic means).

7.2 Results

7.2.1 PCR Analysis of Codon 215 in PBMC

Proviral DNA was detected by nested PCR in the PBMC of 38 of 40 patients after a mean 34 month treatment period. The two patients in whom proviral DNA could not be detected had high CD4 counts at the time their PBMC were analyzed (729 and 676 cells/μl). PCR amplification of the PBMC from 17 of 38 patients (45%) yielded a 210 bp product with the mutant primer, indicating the presence of a mutation at codon 215 (Thr to Tyr or Phe). The PBMC from 21 of 38 patients (55%) demonstrated amplification product only with the wild type primer (a 210 bp product) indicating the presence of Thr at codon 215.

The mean length of therapy and starting CD4 counts for the two groups were similar (Table 2). However, the 17 patients with a mutation at codon 215 of HIV RT in PBMC proviral DNA had a 50% decrease in their absolute CD4 count between the time they began therapy (378 cells/μl) and the end of the study (189 cells/μl). The 21 patients with a wild type sequence at codon 215 experienced a mean 11% increase in their absolute CD4 count between the time they began therapy (397 cells/μl) and the end of the study (424 cells/μl). The post-treatment CD4 percentages of the two groups of patients were also significantly different (25% in patients with wild-type sequence vs 14% in patients with a mutation in RT at codon 215) (Table 2). The CD4 counts at each time point for each patient are shown in FIG. 4.

TABLE 2

CORRELATION OF PATIENT CD4 COUNT CHANGES WITH PCR ANALYSIS OF CODON 215 OF HIV REVERSE TRANSCRIPTASE IN PBMC

Number of patients	Wildtype 21	Mutant 17	p
Months of AZT	33 ± 8	35 ± 7	0.4
Starting CD4 measurements			
Absolute CD4 (cells/μl)	397 ± 124	378 ± 96	>0.5
CD4%	26 ± 8	25 ± 6	>0.5
CD4 measurements at a time of PCR analysis			
Absolute CD4 (cells/μl)	424 ± 210	189 ± 98	<0.0001
CD4%	25 ± 9	14 ± 6	0.0001

7.2.2 PCR Analysis of Codon 215 in HIV RNA from Serum

20 Serial PBMC samples from earlier time points were available on 8/40 patients; however, serial serum samples from earlier time points were available on 37/40 patients. In these 37 patients, 135 serum samples were tested for the presence of a codon 215 mutation. In 87% of these samples (117), reverse transcribed cDNA could be detected by PCR. Fifteen of the 18 sera that were negative by PCR had been previously subjected to multiple freeze-thaws and therefore could be falsely negative. As all patients were AZT-naive, they were assumed to be wild type at codon 215 at the start of AZT therapy.

Twenty-six of the 37 patients developed a mutation in their HIV RNA. This included the 16 who were also mutant in their PBMC at the end of the study period (FIG. 5A), and ten patients who were wild type in their PBMC but mutant in serum HIV RNA at the end of the study period (FIG. 5B). The time preceding the occurrence of the 215 mutation in their serum ranged from 2 to 44 months of therapy. Among these 26 patients, the mean CD4 count at the start of therapy was 398±139 cells/μl and their mean CD4 count at the time of first detection of a codon 215 mutation in their serum was 444±206 cells/μl. Nineteen of the 26 patients with a codon 215 mutation in their serum had follow-up CD4 counts at least 12 months after the mutation was first detected. In these 19 patients, there was a mean decrease of 100±116 CD4 cells/μul (25% decline) at six months and a mean decrease of 170±121 CD4 cells/μl (40% decline) at 12 months.

The 11 patients who remained wild type in their serum over the entire 34 month period of zidovudine therapy had an increase of 7±92 CD4 cells/μl (2% increase), (FIG. 5C). The mean CD4 count at the start of therapy for the patients who later developed a mutant in their serum was 398±139 cells/μl and this was not significantly different than the starting CD4 counts for those patients who remained wild type (397±115 cells/μl, p>0.5). The average length of therapy for both groups was 34 months.

7.2.3 Serum Virus Compared to PBMC Provirus

At the final evaluation of the 38 patients after a mean 34 months of zidovudine, 11 patients were wild type in both serum and PBMC, 17 were mutant in both serum and PBMC, and 10 patients had a mutation in their serum but remained wild type in their PBMC FIG. 6. Eight of the 17 patients with a mutation in proviral DNA at the end of the study period had at least one PBMC sample available from an earlier time point. In these eight patients, a mutation in serum HIV RNA preceded the mutation in proviral DNA by 1-8 months. The findings in these 8 patients and in the 10 patients who were wild type in their PBMC but mutant in their serum shows that detection of the serum mutation precedes detection of the mutation in PBMC. In no instance, did a mutation in patient's PBMC precede its appearance in serum.

7.2.4 AZT Sensitivity Results Determined by Cell Culture

In vitro AZT susceptibility testing was performed on 17 of 38 patients using a different aliquot of the same post-treatment PBMC that were used for the PCR analysis. The geometric mean of the IC_{90}s of eight patients with the wild type form at 215 was 0.04 μm AZT (range: 0.02-0.28 μm); the geometric mean IC_{90} of nine patients with a mutation at codon 215 was 0.41 μm AZT (range: 0.03-8.0 μM; p=0.002).

7.3 Discussion

As an increasing number of HIV infected individuals are offered early treatment with AZT, the significance of drug resistant virus has become an important question. In the present study we found a strong correlation between the presence of a mutation at codon 215, which is linked to AZT resistance and an accelerated decline in CD4 cell number. The patients we studied all began taking AZT when their CD4 cell numbers were relatively high and before the onset of AIDS. We observed that the 17 patients with a mutation at codon 215 in proviral DNA in their PBMC experienced a mean 50% decrease in their CD4 count between the time that they began therapy and the time that their cells were analyzed for mutations. The 21 patients who were wild type at codon 215 in their proviral DNA at the end of treatment experienced a mean 11% increase in their CD4 count during the same time period.

Patient cells were only available during the last year of the study. However, by extracting and reverse transcribing HIV RNA from patient's serum specimens we were able to detect codon 215 mutation at earlier time points. The patients in our study with and without a mutation in serum HIV had similar starting CD4 counts (397±115 vs. 398±139, p>0.5) and similar lengths of therapy (34 months in both groups). Yet we found that those patients who develop a mutation in HIV RNA had a subsequent 40% decline in their CD4 cells over the next 12 months. The patients who remained wild type in their serum had a 2% increase in their CD4 cells over 34 months of therapy.

These results show that genetic changes in the virus which confer drug resistance can be rapidly determined directly form patient PBMC and HIV RNA in patients serum using a nested PCR procedure. By using PCR we were able to detect viral nucleic acid in 90% of PBMC samples and 87% of serum samples. Techniques which require culturing HIV from PBMC or serum may select HIV subpopulations with greater tropism for certain cells (Kusumi et al., 1992, J. Virol. 66:875–885; Meyerhans et al., 1989, Cell 58:901–910). This may complicate the analysis of the clinical significance of AZT resistance detected by phenotypic assays.

Earlier clinical studies focused on AZT resistance in patients with initially low CD4 cell counts or who were at high likelihood of disease progression. Furthermore, these studies tested HIV isolates which had been passaged in culture. In contrast, in this study we did not select patients at high likelihood for disease progression but instead we included all patients who remained on AZT for at least 2 years and who had high CD4 counts at the beginning of the study; codon 215 mutations in serum virus occurred early in treatment. The mean CD4 count at the first appearance of the mutation was higher than the CD4 count at the start of therapy (444 vs. 398 cells/μl). This suggests that mutation of the reverse transcriptase gene is not dependent upon low CD4+ T cells. On the other hand, we also found that a large percentage of patients remained wild type at codon 215 and phenotypically sensitive to AZT despite almost 3 years of therapy. This may be because our patients were less advanced in their disease or that by using PCR instead of coculture we were able to include patients whose virus might not have grown in culture. These results also suggest that the PBMC may not be the initial source of mutant virus, as evidenced in 18 of our patients where the serum HIV RNA mutation preceded that in PBMC by many months. The source of the mutant HIV detected in serum may be cells in lymphatic, central nervous system or reticuloendothial sites.

The significance of specific mutations in the RT gene with respect to AZT resistance has been defined in patient isolates as well as through molecular cloning experiments (Larder et al., 1989, Science 246:1155–1158; Larder et al., 1991, AIDS 5:137–144; Kellam et al., 1992, 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559). Of the four mutations first reported to be associated with AZT resistance (codons 67, 70, 215, 219), the mutation at codon 215 has been shown to be the most commonly occurring and to have the greatest impact on susceptibility. This impact on AZT susceptibility will vary depending on whether or not additional mutations are present (Larder et al., 1989, Science 246:1155–1158; Larder et al., 1991, AIDS 5:137–144; Kellam et al., 1992, 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559; Richman et al., 1991, J. Infect. Dis. 164: 1075–1081; Boucher et al., 1992, J. Infect. Dis. 165:105–110). Recent sequencing studies of clinical isolates suggest that there are additional mutations in the RT gene that may contribute to AZT resistance (Japour et al., 1991, Proc. Natl. Acad. Sci. 88:3092–96; Kellam et al., 1992, Proc. Natl. Acad. Sci. USA 89:1934–1938; St. Clair et al., 1991, Science 253:1557–1559). However, the occurrence of the two consecutive nucleotide changes necessary for the amino acid change at codon 215 may be the most important requirement for the development of resistance (Kellam et al., 1992, Proc. Natl. Acad. Sci. U.S.A. 89:1934–1938; Richman et al., 1991, J. Infect. Dis. 164:1075–1081; Boucher et al., 1992, J. Infect. Dis. 165:105–110). In this study, a subset of 17 patients were tested using a cell culture assay which confirmed that the viruses with a mutation at codon 215 had reduced susceptibility to AZT.

The patients with resistant or sensitive virus in our study had similar CD4 counts at the start of AZT therapy and received AZT for a similar period of time. Therefore, the development of resistance and a mutation at codon 215 could not be attributed to any known pretreatment characteristic. None of our patients developed AIDS during our study period and the patients who developed a mutation in their serum HIV RT did so at a relatively high CD4 count. Thus, advanced stage of HIV disease could not explain why some patients developed a mutation while others did not. Additional characteristics of the patient or virus may explain why one HIV strain develops a mutation and another does not. It has been stated that syncytium-inducing, T-cell tropic isolates in HIV-infected individuals contribute to the CD4 cell decline (Tersmette et al., 1989, Lancet 1:983–985). If an HIV isolate can maintain a high level of replicative events despite the presence of AZT, this virus would have a much greater likelihood of mutation. Treatment with AZT may select both syncytium-inducing and drug resistant virus. Selection of more virulent HIV population under prolonged AZT pressure may explain why some patients experienced a CD4 cell decline in the months after the RT mutation arose.

The present report shows a strong association between the presence of a HIV RT mutation and declining CD4 counts in AZT treated patients. Furthermore, it demonstrates that a HIV mutation known to cause AZT resistance can be detected prior to a decline in CD4 cell number.

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What is claimed is:

1. A method of evaluating the effectiveness of anti-HIV therapy of a patient comprising:

correlating the presence or absence of detectable HIV-encoding nucleic acid in a plasma sample of an HIV infected patient with an absolute CD4 count, wherein the presence or absence of said detectable HIV-encoding nucleic acid is determined by

(i) collecting a plasma samples from an HIV-infected patient who is being treated with an antiretroviral agent;

(ii) amplifying HIV-encoding nucleic acid that may be present in the plasma sample using HIV primers via PCR and;

(iii) testing for the presence of HIV-encoding nucleic acid sequence in the product of the PCR.

2. The method of claim 1, wherein the absence of HIV-encoding nucleic acid and the absolute CD4 count being greater than about 200 cells per cubic millimeter correlate positively with the conclusion that the antiretroviral agent is therapeutically effective.

3. The method of claim 1, wherein the presence of HIV-encoding nucleic acid and the absolute CD4 count being less than about 200 cells per cubic millimeter correlate positively with the conclusion that the antiretroviral agent is therapeutically ineffective.

4. The method of any one of claims 1-3, wherein the PCR is performed for about 30 cycles.

5. The method of any one of claims 1-3 in which the HIV primers are SK38 and SK39.

6. The method of any one of claims 1-3 in which one HIV primer is primer NE1 (5'TCATTGACAGTCCAGCT-3') (SEQ ID NO:2).

7. The method of any one of claims 1-3 in which one HIV primer is primer A (5'-TTCCCATTAGTCCTATT-3') (SEQ ID NO:1).

8. The method of any one of claims 1-3 in which the antiretroviral agent is zidovudine.

* * * * *

PETITIONER'S BRIEF

10

Supreme Court, U.S.
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DEC 16 2010
OFFICE OF THE CLERK

No. 09-1159

IN THE

Supreme Court of the United States

BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY,

Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF PETITIONER

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December 16, 2010

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(96)

QUESTION PRESENTED

Whether a federal contractor university's statutory right under the Bayh-Dole Act, 35 U.S.C. §§ 200-212, in inventions arising from federally funded research can be terminated unilaterally by an individual inventor through a separate agreement purporting to assign the inventor's rights to a third party.

PARTIES TO THE PROCEEDING

The parties to the proceeding in the Court of Appeals for the Federal Circuit were Petitioner Board of Trustees of the Leland Stanford Junior University and Respondents Roche Molecular Systems, Inc.; Roche Diagnostics Corporation; and Roche Diagnostics Operations, Inc.

CORPORATE DISCLOSURE STATEMENT

Petitioner Board of Trustees of the Leland Stanford Junior University has no parent corporation and does not issue stock.

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OPINIONS BELOW

The decision of the United States Court of Appeals for the Federal Circuit, Pet. App. 1a-28a, is reported at 583 F.3d 832. The opinion of the United States District Court for the Northern District of California on the issue of Petitioner's standing to sue for patent infringement, Pet. App. 29a-74a, is reported at 487 F. Supp. 2d 1099.

JURISDICTION

The Court of Appeals issued its decision on September 30, 2009. The Petition for Panel Rehearing and Rehearing *En Banc* was denied on December 22, 2009. Pet. App. 75a-77a. The petition for a writ of certiorari was filed on March 22, 2010, and granted on November 1, 2010. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS INVOLVED

The text of the University and Small Business Patent Procedures Act of 1980, commonly known as the Bayh-Dole Act, 35 U.S.C. §§ 200-212, is set forth in the appendix to this brief.

STATEMENT

This case turns on construction of the Bayh-Dole Act's provisions governing ownership of inventions arising from federally funded research. That Act was the product of decades of experience with prior statutory regimes. It creates a uniform hierarchy in which federal contractor grantees are given the first right to perfect title in the invention. The federal Government holds explicit powers to enforce the statute's objectives, including itself receiving title if the contractor elects not to or defaults in ways specified in the statute. Individual inventors may get

title only in specified circumstances, if it is not retained by either the contracting institution or the Government.

A. The State of the Law Before the Bayh-Dole Act

1. Prior to passage of the Bayh-Dole Act in 1980, the Government had no uniform policy to determine the ownership of patents arising out of federally supported research. Instead, a "mélange of 26 different agency policies" governed who acquired title to Government-funded inventions. H.R. Rep. No. 96-1307, pt. 1, at 3 (1980), *reprinted in* 1980 U.S.C.C.A.N. 6460, 6462.[1] Although each of the twenty-six policies differed in certain specifics, they generally followed one of two approaches. One approach favored vesting of title in the Government, and the second favored leaving title in the private entities that performed the federally funded research, subject to the Government's retention of a license to itself practice the patent.

The title approach was motivated by a view that the public interest was best served by Government ownership of patents resulting from federally funded research. "Where patentable inventions are made in the course of performing a Government-financed contract for research and development, the public interest requires that all rights to such inventions be assigned to the Government and not left to the

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[1] A breakdown of most agencies' policies can be found in Subcomm. on Domestic and Int'l Scientific Planning and Analysis, H. Comm. on Sci. & Tech., 1 *Background Materials on Government Patent Policies: Presidential Statements, Executive Orders, and Statutory Provisions* 61-85 (1976).

private ownership of the contractor." Francis Biddle, Att'y Gen., 1 *Investigation of Government Patent Practices and Policies: Report and Recommendations of the Attorney General to the President* 4 (1947). Several agencies followed such a title policy by statute or regulation. *See, e.g.*, Federal Non-nuclear Energy, Research, and Development Act ("FNERDA") of 1974, Pub. L. 93-577, § 9, 88 Stat. 1878, 1887-88. According to the Federal Circuit, these statutes and regulations clearly "divested" inventors or other private entities "of all [their] interest." *FilmTec Corp. v. Hydranautics*, 982 F.2d 1546, 1553 (Fed. Cir. 1992) (applying FNERDA to bar an inventor's assignment).

The license approach stemmed from a preference that the Government acquire only those rights necessary to enable it to practice the invention rather than take full ownership of patents, on the view that leaving ownership with the contractor was the most effective way to advance innovation and achieve utilization and enforcement of patent rights. *See* Nat'l Patent Planning Comm'n, *Government-Owned Patents and Inventions of Government Employees and Contractors*, *reprinted in* 23 Chem. & Eng'g News 438, 442 (1945). For example, the Department of Defense followed a license policy, contending that it was the only way to ensure that the best contractors would participate in the development process. *See Science and Technology Research and Development Utilization Act: Hearing Before the Subcomm. on Sci., Tech., & Space, of the S. Comm. on Commerce, Sci. & Transp.*, 96th Cong. 364-65 (1979) (statement of Dale W. Church, Deputy Under Secretary of Defense for Acquisition Policy) (hereinafter "Church statement"). Still, the license

policy recognized the Government's ultimate control over inventions that resulted from federal funding, because it conferred title on the contracting entity, not the inventor, and demanded that the entity grant the Government an irrevocable paid-up license (*i.e.*, without payment of any additional federal funds) as a condition of retaining title. *See Mead Corp. v. United States*, 490 F. Supp. 405, 407-08 (D.D.C. 1980) (noting that the inventor only had title by virtue of the contractor's policies, *cf.* 32 C.F.R. § 9.107-2(b), ¶ (e) (1961)), *aff'd*, 652 F.2d 1050 (D.C. Cir. 1981).

While the policies differed in approach, each was premised upon the pre-eminent right of the Government to establish ownership of intellectual property created by public investment. They differed only on how best to use that right in furtherance of the public interest. Advocates of a title policy argued that the public was entitled to the fruits of its investment. *See Science and Technology Research and Development Utilization Act: Hearing Before the Subcomm. on Sci., Tech., & Space of the S. Comm. on Commerce, Sci. & Transp.*, 96th Cong. 397 (1979) (statement of Adm. Hyman G. Rickover, Deputy Commander for Nuclear Propulsion, Department of the Navy). Those in favor of a licensing policy contended that private ownership was necessary both to encourage industry to participate in research, and to ensure the commercialization and general availability of the research results. *See* Church statement, *supra*, at 368.

2. The debate over which approach to use continued for more than thirty years. From 1945 to 1980, numerous congressional reports studied the issues, and numerous bills were proposed to govern

who owned the intellectual property that resulted from federally funded research. *See* Subcomm. on Domestic and Int'l Scientific Planning and Analysis of the H. Comm. on Sci. & Tech., 2 *Background Materials on Government Patent Policy: Reports of Committees, Commissions, and Major Studies* (1976); James A. Dobkin, *Patent Policy in Government Research and Development Contracts*, 53 Va. L. Rev. 564, 630-46 (1967) (detailing four different bills debated, but not passed, from 1965 to 1966 alone). But no uniform policy was enacted at that time.

President Kennedy's Government Patent Policy Memorandum, adopted October 10, 1963, came closest to creating Government-wide uniformity. *See* Government Patent Policy, 28 Fed. Reg. 10,943 (Oct. 12, 1963). That Memorandum again recognized the pre-eminent "responsibility" of the Government "to foster the fullest exploitation of the inventions for the public benefit." *Id.*

Rather than choosing between a title policy or a license policy, President Kennedy attempted to accommodate both sides of the debate by encouraging agencies to tailor their approach to the invention at issue. The memorandum encouraged a title policy "where the nature of the work to be undertaken or the Government's past investment in the field of work favors full public access to resulting inventions." *Id.* A license policy, by contrast, was appropriate "where the contractor has an established non-governmental commercial position and where there is greater likelihood that the invention would be worked and put into civilian use than would be the case if the invention were made more freely available." *Id.*

3. The Department of Health, Education, and Welfare ("HEW") followed the mixed title-license policy called for in the Kennedy Memorandum, and its experience is particularly relevant here for several reasons. First, HEW is the former parent department of the National Institutes of Health ("NIH"), whose funding underwrote the Stanford research at issue in this case. Second, the changes in how HEW applied its policies, which are detailed below, provided an important impetus for the enactment of the Bayh-Dole Act. Finally, Bayh-Dole is modeled, in part, on HEW's Institutional Patent Agreements ("IPAs"), which are described below.

A single set of HEW regulations, with immaterial amendments, governed the agency's patent policy from 1955 to 1979. *Compare* 45 C.F.R. Part 8 (1957 Cum. Supp.) *with id.* (1979). Those regulations, like President Kennedy's Memorandum, asserted a pre-eminent public interest in all inventions created as the result of research supported by federal funds. "[T]he results of research supported by grants of public moneys should be utilized in the manner which would best serve the public interest." *Id.* § 8.0(b).

Rather than adopting a title policy or a license policy to govern all funded research, the regulations generally reserved the decision of how to allocate patent rights until after invention. *Id.* § 8.1(a). Under this general approach, there was a rebuttable presumption that title would vest in the Government. *Id.* § 8.2(d). One limited exception to this after-the-fact determination created a license policy at the inception of the research if the agency determined that "the grantee's established policies and

procedures" were "such as to assure that the invention will be made available without unreasonable restrictions or excessive royalties." *Id.* § 8.1(b). HEW implemented this limited exception by entering into IPAs with certain grantees to delineate the respective rights of the private but federally funded institution and HEW.

Even though HEW had the same general regulations for twenty-four years, the agency's actual practices differed markedly within this time. Initially, HEW rarely used its regulatory authority to waive title to federally funded patents, either post-invention under § 8.2(a)-(b) or with IPAs under § 8.1(b). *See* Memorandum from James A. Shannon, Director of the National Institutes of Health, to the Surgeon General 1 (Aug. 14, 1964); Rebecca S. Eisenberg, *Public Research and Private Development*, 82 Va. L. Rev. 1663, 1682-83 (1996) (describing an expansion of HEW's title policy in 1962).

In 1968, however, HEW changed its practices in response to criticism that it had not provided sufficient rights to grantees to ensure participation in federally funded research. *See* Harbridge House, Inc., 2 *Government Patent Policy Study* 2-40 (1968); Comptroller Gen., *Problem Areas Affecting Usefulness of Research of Government-Sponsored Research in Medicinal Chemistry* 31-32 (1968). HEW revamped and standardized its IPAs, which delegated to grantees authority to elect patent rights subject to a Governmental license pursuant to 45 C.F.R. § 8.1(b). Consistent with the license policy, the new form IPA gave grantees "a first option to retain principal rights in and to administer

inventions." HEW, Institutional Patent Agreement: Revised Draft pmbl. (July 11, 1968); *cf.* 45 C.F.R. § 8.1(b). Within a year, HEW entered into twenty-one such agreements, compared to only seventeen between 1955 and 1967. Manuel B. Hiller, HEW, *Government View*, in Nat'l Acad. of Eng'g, *Government Patent Policy* 9, 15 (1969). Additionally, post-invention "determinations were made to leave invention rights to grantee institutions in 13 cases in calendar year 1968 alone," compared with "only five instances during the 12-year period from 1953 to 1965." *Id.*; *cf.* 45 C.F.R. § 8.2(a)-(b).

The 1968 policy changes achieved significant success in the scientific fields funded by HEW. "Since instituting the I.P.A. program a number of potentially important new drugs initially funded under HEW research have been delivered to the public through the involvement of private industry .... This program has been so successful that it has been copied by other agencies ... and was approved by the General Services Administration in 1978 ... ." S. Rep. No. 96-480, at 21 (1979); *cf.* Federal Procurement Regulations Amendment 187, 43 Fed. Reg. 4424 (Feb. 2, 1978).

"Ironically, HEW [returned] to its pre-1968 patent policies" under the Carter Administration. S. Rep. No. 96-480, at 21 (1979). In 1977, the new Secretary of HEW halted the routine approval of title waivers and IPAs. *See* Roberto Mazzoleni, *Patents and University-Industry Interactions in Pharmaceutical Research Before 1962*, 10 J. High Tech. L. 168, 183 (2010). This change "mobilized universities and other R&D contractors of the federal government in support of the Bayh-Dole Act, which is

widely credited for making its passing possible in 1980." *Id.*; *cf.* S. Rep. No. 96-480, at 21 (1979).

4. HEW's experience reflects some of the problems confronted under both the title and license policies. Title policies discouraged industrial participation, as HEW experienced before 1968. Moreover, even if inventions were made, the Government often was not able to commercialize them due to the additional costs necessary to develop an invention to the point of utilization. *See* S. Rep. No. 96-480, at 3 (1979) (noting that only 4% of Government-held patents were commercialized); 126 Cong. Rec. 29,896 (1980) (estimating the additional costs of development to be ten times as much as the original invention). Thus, under a title policy, patents gathered dust on Government shelves and industry was reluctant to undertake new research.

License policies avoided some of these problems but had their own defects. While contractor-held inventions were nine times more likely to be commercialized, *see* S. Rep. No. 96-480, at 3 (1979), the fact that the licensing policies were a matter of administrative grace, subject to change with each new administration, created uncertainty that dampened enthusiasm in the private sector. *Industrial Innovation and Patent and Copyright Law Amendments: Hearing Before the Subcomm. on Courts, Civil Liberties, and the Admin. of Justice, H. Comm. on the Judiciary,* 96th Cong. 67 (1980) (statement of Dr. Roy P. Vagelos, President of Merck Sharp & Dohme Research Labs.); *see also* 126 Cong. Rec. 8739 (1980) (Sen. Dole).

The lack of statutory authority for the license policies posed an additional problem. One court invalidated licensing regulations as violating the constitutional prohibition on the disposition of Government property without congressional approval. *Public Citizen, Inc. v. Sampson*, 180 U.S.P.Q. 497 (D.D.C. 1974). While this holding was ultimately vacated for lack of standing, 515 F.2d 1018 (D.C. Cir. 1975), the suit nonetheless raised questions regarding the constitutionality of agency-initiated policies assigning title to the contractor. *See* Memorandum from Roger C. Cramton, Ass't Att'y Gen., Office of Legal Counsel, to Bruce B. Wilson, Deputy Ass't Att'y Gen., Antitrust Division, *Constitutionality of Proposed Regulations Granting Contractors Greater or Principal Rights Arising Out of Government Research and Development Contracts* (Oct. 10, 1972), *reprinted in* 119 Cong. Rec. 40,417-20 (1973).

Moreover, the existence of dueling license and title approaches, and over twenty-six different agency policies, posed additional administrative problems. "The mere complexity of these policies constitute[d] a very real hurdle to universities, nonprofit organizations, and small businesses who do not have large legal staffs to negotiate through this policy maze." S. Rep. No. 96-480, at 2-3 (1979). Further, when, as was often the case, funding came from multiple agencies, there was no clear rule as to which policy (or policies) should govern.

B. Bayh-Dole's Enactment: Purposes, Text, and Regulations

Against the confusion created by dozens of separate vesting statutes and divergent policies, Congress passed the Bayh-Dole Act in 1980, creating, for nonprofit organizations and small business firms, a uniform hierarchy of rights for inventions arising from Government-funded research. The Act gave private institutions a first right of refusal to receive title; the Government was the enforcer of the statute's requirements, with a full license and the possibility of itself receiving title in specified circumstances; and inventors were expressly given rights to royalties and the possibility of ultimately receiving title, subject to all of the Act's requirements, if it is concluded that title should not reside in either the private institution or the Government. Finally, uniform implementing regulations, detailing the Act's applicability to all funding arrangements, actuated Bayh-Dole's purposes and goals.

1. Section 200 of the Act details "the policy and objective of the Congress." 35 U.S.C. § 200. Most fundamentally, the Act reflects a statutory commitment to "use the patent system to promote the utilization of inventions arising from federally supported research or development" to foster the "public availability of inventions made in the United States by United States industry and labor." *Id.* In order to achieve this goal, that statute sought "to ensure that the Government obtains sufficient rights" not only to meet its own needs, but to "protect the public against nonuse or unreasonable use of inventions." *Id.* The Act also sought to "promote

collaboration between commercial concerns and nonprofit organizations, including universities," "encourage maximum participation of small business firms" in Government research, "ensure" that inventions by such institutions "are used in a manner to promote free competition and enterprise," and "minimize the costs of administering policies in this area." *Id.*

2. The over-arching title of the Bayh-Dole Act, as enacted and as it appears in the United States Code, is "Patent Rights in Inventions Made With Federal Assistance." 35 U.S.C. ch. 18. Section 202, the main operative provision, details the "[d]isposition of rights" to any "subject invention," a term that the Act defines as "any invention of the contractor[2] conceived or first actually reduced to practice in the performance of work under a funding agreement." *Id.* § 201(e). This disjunctive definition uses familiar terms that had been interpreted broadly during their use as part of the licensing approach of the Department of Defense. *See, e.g.*, Theodore Prahinski, *Interpretation of Term 'First Actually Reduced to Practice' Used in Patent Rights Clauses of Government Contracts*, 55 J. Pat. Off. Soc'y 107, 108 (1973). And, as the definition of "funding agreement" makes clear, Bayh-Dole's operative provisions apply where the "research work [is] funded in whole or in part by the Federal Government." 35 U.S.C. § 201(b).

Section 202(a) contains the critical right to take title at issue in this case: "[e]ach nonprofit

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[2] "The term 'contractor' means any person, small business firm, or nonprofit organization that is a party to a funding agreement." *Id.* § 201(c).

organization or small business firm may ... elect to retain title to any subject invention." *Id.* § 202(a).[3] In order to obtain this title, however, the institution must comply with a number of procedural requirements that § 202(c) directs must be set forth in the funding agreement: the institutions must "disclose each subject invention to the Federal agency within a reasonable time," must "make a written election within two years after disclosure ... whether the contractor will retain title," and must "file a patent application prior to any statutory bar date." *Id.* § 202(c)(1)-(3). If the institution fails to comply with any one of these provisions, the statute specifically provides that "the Federal Government may receive title." *Id.*

Where the contractor elects to retain title, it has several other obligations as well. It must report on the utilization of the subject invention as required by the federal agency, and must state in the patent specification that the invention was made with Government support, thereby putting the world on notice of the Government's rights. *Id.* § 202(c)(5)-(6). The Act also limits the ability of a nonprofit organization to assign its rights to a subject invention, *id.* § 202(c)(7)(A), and requires that any net royalties or other income remaining with the

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[3] The contractor's ability to retain title is subject to being restricted in the funding agreement, as discussed at length in 35 U.S.C. § 202(a). Among other stated grounds for including a provision in the agreement limiting the contractor's right to retain title are "exceptional circumstances when it is determined by the agency that restriction or elimination of the right to retain title to any subject invention will better promote the policy and objectives of this chapter." *Id.* § 202(a)(ii).

contractor after it makes various required payments "be utilized for the support of scientific research or education." *Id.* § 202(c)(7)(C). Also, the contractor is generally barred from granting an exclusive license absent agreement by the licensee that products under the license "will be manufactured substantially in the United States." *Id.* § 204.

In addition to the Government's ultimate right to itself "receive title" in the case of a contractor's non-election or non-compliance with certain requirements, it retains important rights and powers even where title is successfully retained by the contractor. First, the Government agency "shall have a nonexclusive, nontransferable, irrevocable, paid-up license to practice ... [the] subject invention." *Id.* § 202(c)(4). Second, related to the contractor's duty to report on its progress in achieving utilization of the invention, *id.* § 202(c)(5), the agency has "[m]arch-in rights," which entitle it, under certain circumstances, to grant, or require the contractor (or its assignee or exclusive licensee) to grant, a license to a responsible third party. *Id.* § 203.

The rights of inventors relating to a "subject invention" are expressly defined in the statute. The Act provides that, where the contractor is a non-profit organization, the funding agreement itself must require the contractor to "share royalties with the inventor." *Id.* § 202(c)(7)(B). And where the "contractor does *not* elect to retain title," the Government "may consider and after consultation with the contractor grant requests for retention of rights by the inventor subject to the provisions of this Act and regulations promulgated" under it. *Id.* § 202(d) (emphasis added). Receipt of such title by

the inventor, subject to all the same requirements as govern a contractor retaining title, would thus occur only where the Government decides not to "receive title" itself. *Id.* § 202(c)(2).

In sum, Bayh-Dole "entrusted" nonprofits and small businesses with patent ownership to act "as a steward of the public interest. Universities are expected to reasonably represent these interests, reaching 'win-win' deals with private sector developers." Birch Bayh, Joseph P. Allen, and Howard W. Bremer, *Universities, Inventors and Bayh-Dole*, 79 Pat., Trademark & Copyright J. 167, 169 (2009).

3. Bayh-Dole's first implementing regulations were promulgated within a year of the statute's enactment.[4] Issued as Bulletin 81-22, the regulations made clear that Bayh-Dole "coupled" the Government's investment in research with "the incentive of invention ownership in small businesses, non-profits and universities." Patents; Small Firms and Non-Profit Organizations, 46 Fed. Reg. 34,776, 34,776, ¶ 3 (July 2, 1981).

After the agency received public comments on the Bulletin, it promulgated Circular A-124 in 1982. *See* Patents—Small Firms and Non-Profit Organizations, 47 Fed. Reg. 7556 (Feb. 19, 1982). The Circular stated that Bayh-Dole "gives nonprofit organizations

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[4] *See* 35 U.S.C. § 206 (1982) (empowering the Office of Federal Procurement Policy to "issue regulations ... implementing the provisions of sections 202 through 204 of this chapter"), *amended by* Pub. L. 98-620, § 501(10), 98 Stat. 3335, 3367 (1984) (transferring regulatory authority to the Department of Commerce).

and small businesses ... a first right of refusal to title in inventions they have made in performance of Government grants and contracts." *Id.* at 7559, ¶ 4.

The current regulations, issued by the Department of Commerce and codified at 37 C.F.R. Part 401, maintain this interpretation. Indeed, the bulk of the current regulations track, word-for-word, Circular A-124. *Compare, e.g.*, 37 C.F.R. § 401.1(a) (2010) *with, e.g.*, 47 Fed. Reg. at 7557.

C. Background of the Case

1. This dispute concerns the ownership of three patents claiming methods for evaluating the effectiveness of treatments for Human Immunodeficiency Virus ("HIV"), the virus that causes AIDS: U.S. Patent Nos. 5,968,730 ("the '730 Patent"); 6,503,705; and 7,129,041-B2. Three Stanford researchers—Drs. Merigan, Katzenstein, and Holodniy—developed these methods and are the named inventors. Pet. App. 125a-132a. Stanford is also named on the patents, as the inventors' assignee. *Id.* Because two NIH grants for AIDS-related work provided partial funding for Stanford's research, each patent states that "[t]his invention was made with Government support under contracts AI27762-04 and AI27766-07, awarded by the National Institutes of Health. The Government has certain rights in this invention." *Id.* at 126a, 128a, 132a.

The ownership dispute arises from agreements signed by one of the named inventors, Dr. Holodniy. On joining Stanford's Department of Infectious Disease in July of 1988, Dr. Holodniy signed Stanford's standard Copyright and Patent Agreement. Pet. App. 94a. He specifically "agree[d]

to assign ... to Stanford" his intellectual property rights "as required by Contracts or Grants." Pet. App. 119a. The Agreement prohibited Dr. Holodniy from "enter[ing] into any agreement creating copyright or patent obligations in conflict with this agreement." Pet. App. 120a.

In the fall of 1988, Dr. Holodniy "joined the [Stanford] lab of Dr. Thomas Merigan" as a research fellow and assisted with research directed "to developing a better quantitative PCR-based assay[5] for HIV than the one that existed at that time." Pet. App. 94a. At the time Dr. Holodniy joined the lab, this work was already being supported by research funding from NIH. JA 95, 98. Dr. Holodniy's initial work at Stanford experimented with PCR assays on HIV sequences, attempting to measure the amount of HIV DNA in a patient taking antiretroviral drugs in order to determine the effectiveness of the treatment.[6] *See* Pet. App. 34a.

After Dr. Holodniy spent several months working on the federally funded research at Stanford, his supervisor suggested that he visit Cetus, a local

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[5] PCR, or polymerase chain reaction, is a technique that makes it easier to evaluate genetic material by creating millions of copies of DNA or RNA segments from a small sample.

[6] HIV is a retrovirus, which means that it has an RNA genome rather than the DNA genome typical of most viruses. HIV virions bind to the CD4 protein on the surface of certain immune cells and inserts its contents, including its RNA genome, into the cells. The HIV RNA is converted to DNA, which is then integrated into the CD4 cell's genomic DNA. This integrated, "proviral" DNA reprograms the CD4 cells to produce additional HIV particles, ultimately killing the infected CD4 cell and releasing more HIV virions.

biotechnology company. Pet. App. 35a. PCR had been invented at Cetus in the mid-1980s. JA 37. Cetus agreed, and Dr. Holodniy spent time both working at Stanford and visiting Cetus for approximately nine months in 1989. Pet. App. 95a-96a.

In connection with Dr. Holodniy's visits, Cetus asked him to sign a "Visitor's Confidentiality Agreement" ("VCA"). Pet. App. 122a-124a. In this agreement, Dr. Holodniy acknowledged that he might "acquire techniques, know-how, or other information of a confidential nature." Pet. App. 122a. As suggested by the Agreement's title, Dr. Holodniy promised "NOT [TO] DISCLOSE ANY SUCH INFORMATION TO ANY PERSON OR ENTITY ... WITHOUT CETUS' PRIOR WRITTEN CONSENT." Pet App. 123a.

A subsequent provision in the VCA stated that Dr. Holodniy "hereby assign[ed] to Cetus my right" to any inventions conceived or reduced to practice "as a consequence of my access to Cetus's facilities or information." Pet. App. 123a-124a. Dr. Holodniy "understood that the agreement concerned my obligations to Cetus' confidential information," but he also understood that nothing he ultimately learned at Cetus was of a confidential nature. Pet. App. 95a-97a.

2. Dr. Holodniy visited Cetus several days a week beginning in February 1989, while also continuing his work at Stanford. Pet App. 95a-96a. After the first several months at Cetus, Dr. Holodniy and his Stanford supervisors decided, "without any input from Cetus scientists," to shift to trying to

quantify HIV RNA in plasma, rather than HIV DNA in cells. Pet. App. 100a. Dr. Holodniy then developed a workable PCR assay to quantify HIV RNA. Pet. App. 98a-100a. While Cetus scientists helped Dr. Holodniy by providing, at his direction, assistance relating to the comparison standard for quantification, each of the PCR steps of the assay Dr. Holodniy developed was publicly available at the time. Pet. App. 97a-100a; JA 39-40.

To share his work, Dr. Holodniy—along with Stanford and Cetus co-authors—published an article describing it. The article noted that the research was funded in part by Stanford's federal grants and expressed hope that "[s]erum PCR may provide an additional marker of disease progression." Mark Holodniy *et al.*, *Detection and Quantification of Human Immunodeficiency Virus RNA in Patient Serum by Use of the Polymerase Chain Reaction*, 163 J. Infectious Diseases 862, 862, 865 (1991) ["JID Article"]; JA 135, 148-49. It concluded, however, by noting that "[f]urther studies will be necessary to validate this approach." *Id.* at 865; JA 149. Cetus approved the JID Article for publication and did not file any patent application or otherwise seek ownership over the assay disclosed in the article. In fact, Cetus's patent committee had given the work its lowest possible rating for patentability or commercial development. Pet. App. 38a.

When Dr. Holodniy ceased visiting Cetus and resumed full-time activity at Stanford in October or November of 1989, he and Drs. Merigan and Katzenstein performed extensive studies and clinical experiments, using real-life patient monitoring of persons taking anti-HIV therapy. Pet. App. 102a-

104a. This work was done without any further involvement or assistance from Cetus. *Id.* In their research, the Stanford team faced a number of significant challenges:

> [T]here was widespread uncertainty at the time about whether the assay [could] be sufficiently sensitive and reproducible to measure HIV RNA changes over time in a clinical setting. It was unclear whether the variability of virus levels and changes in virus levels for different individuals would be detectable using this assay. There was much uncertainty in the field about whether nucleic acid levels in plasma could be used to predict the effectiveness of the therapy. There was also an overriding concern about whether the available treatments would be strong enough to produce changes that could be measured.

Pet. App. 103a. Additionally, "[t]he quantitative assay needed more refinement to improve sensitivity and reproducibility." *Id.* Accordingly, the Stanford team performed numerous experiments and extensive statistical analyses to develop a therapeutically useful technique and protocol. Pet. App. 103a-104a.

Ultimately, in 1991, the Stanford team was able to develop a technique for monitoring the effectiveness of anti-HIV therapy based on the results of their clinical research. *Id.* The team published an article in the Journal of Clinical Investigation

detailing their results and acknowledging the Federal funding of the research. Mark Holodniy *et al.*, *Reduction in Plasma Human Immunodeficiency Virus Ribonucleic Acid After Dideoxynucleoside Therapy as Determined by the Polymerase Chain Reaction,* 88 J. Clinical Investigation 1755, 1759 (1991) ["JCI Article"]. Stanford filed a patent application on May 14, 1992. Pet. App. 108a.

Because the work done by the Stanford researchers was funded by the NIH, the resulting discovery was a "subject invention" governed by the Bayh-Dole Act. 35 U.S.C. § 201(e). Pursuant to the Act's provisions, Stanford timely submitted an invention disclosure form to the NIH in 1992 and confirmed the grant of a nonexclusive, nontransferable, irrevocable, paid-up license in the patent application to the Government as required. *See* Pet. App. 5a-6a; *see also* 35 U.S.C. § 202(c)(1), (4). In 1995, also pursuant to Bayh-Dole, Stanford timely perfected its rights to the patent by formally notifying the Government that it elected to retain title. Pet. App. 115a-116a.; *see also* 35 U.S.C. § 202(c)(2).[7] It is undisputed that Stanford has satisfied all requirements of the Bayh-Dole Act to perfect its title to the subject inventions.

3. Cetus's PCR-related assets were acquired by Hoffmann-La Roche, Inc., a Swiss pharmaceutical company, in 1991. Pet. App. 42a. At no time prior to that acquisition did Cetus advise Stanford of the VCA

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[7] Shortly after making its election to retain title, Stanford recorded with the Patent and Trademark Office new assignments from Drs. Merigan, Katzenstein, and Holodniy relating specifically to this invention. Pet App. 41a, 112a.

or of any claim to own the inventions of the patents-in-suit. Nor did Roche make any filing relating to an interest in those inventions based on the VCA during the pendency of the patent applications pertaining to the patents-in-suit. Likewise, no such notice was given to Stanford or any involved party at or following the issuance of any of the patents, even though Roche learned of the first of these, the '730 patent-in-suit, soon after it issued in 1999. Pet. App. 41a.

In 2000, Luis Mejia, a Senior Licensing Associate in Stanford's Office of Technology Licensing, traveled to Basel, Switzerland, to offer "Roche an exclusive license to the '730 patent and related Stanford patents." Pet. App. 109a-110a. Throughout the presentation, "it was clear that Stanford did not recognize that either Cetus or Roche had any ownership or license interest" in the '730 patent-in-suit. *Id.* Roche did not suggest otherwise: "no one from Roche ever indicated ... that Roche believed it had any right of ownership or license." *Id.* Instead, Roche negotiated with Stanford over a possible licensing arrangement for the next four years. Pet. App. 6a.

4. No licensing arrangement was reached. In 2005, Stanford sued Roche for infringement, based in part on Roche's sales of kits used to evaluate the effectiveness of anti-HIV therapy. Roche answered and counterclaimed, asserting, in relevant part, that it possessed an ownership interest in the patents because of Dr. Holodniy's assignment in the Visitor Confidentiality Agreement. *See, e.g.*, Defs.' Answer & Countercl. (D. Ct. Dkt. No. 15) 12, 18.

The district court bifurcated the ownership and infringement issues. On cross-motions for summary judgment, Judge Patel rejected Roche's ownership claims on several grounds, two of which are relevant here. First, she held that both California's four-year statute of limitations and the doctrine of laches barred Roche from asserting an ownership claim more than four years after it had learned of the patent. Pet. App. 48a-52a ("[b]ecause Roche's delay in suing to enforce its ownership interest is unreasonable and has at least caused substantial evidentiary prejudice to Stanford, Roche's ownership claims are barred by the doctrine of laches").

As a second, independent ground for rejecting Roche's arguments, the district court held that "Holodniy's purported assignment to Cetus conflicted with the legal requirements of the Bayh-Dole Act, which mandated that Stanford be given a superior right to retain title to the patents." Pet. App. 62a. Under Bayh-Dole, Dr. Holodniy "had no interest to assign." *Id.*

After the Federal Circuit denied mandamus review of the ownership ruling, 513 F.3d 1003 (Fed. Cir. 2008), the district court granted Roche summary judgment on the infringement issue, holding that the patents were obvious, focusing primarily on Dr. Holodniy's JID Article. 563 F. Supp. 2d 1016 (N.D. Cal. 2008).

Stanford appealed the obviousness ruling, and Roche cross-appealed on the ownership claim. The Federal Circuit did not reach Stanford's appeal. Instead, while agreeing with the district court that Roche's affirmative claim of ownership was barred by

the statute of limitations, Pet. App. 9a, the court determined that Roche's lengthy delay did not bar it from asserting its ownership as a defense, and in particular from "assert[ing] its ownership interest as a bar to Stanford's standing." Pet. App. 12a.

The Federal Circuit further held that Cetus's VCA, acquired by Roche, trumped both Stanford's earlier Copyright and Patent Agreement and the later recorded assignment. Pet. App. 12a-14a. Reasoning that the "agree to assign" language of the earlier assignment to Stanford "reflects a mere promise to assign rights in the future," while the "do hereby assign" language of the VCA "effected a present assignment of Holodniy's future inventions to Cetus," the court concluded that "Cetus's equitable title converted to legal title no later than the parent application's filing date" in 1992, and takes priority over Stanford's earlier assignment agreement. Pet. App. 13a-14a.

The court also ruled that the premise of the VCA—that the invention be developed "as a consequence of [Dr. Holodniy's] access to CETUS' facilities or information"—was satisfied because Dr. Holodniy at Cetus received access to certain information, materials and equipment, which were used in the development of the invention.[8] Pet. App. 15a, 123a. The Court made clear that its ruling rested simply on the fact that Cetus's information or facilities contributed in some way to the ultimate invention, and did not depend on any finding that

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[8] The court below does not suggest that anything received or used by Dr. Holodniy at Cetus was confidential, or that such confidentiality was necessary for the assignment to be effective.

property—*i.e.*, a patentable invention—had been created by the work Dr. Holodniy was involved in at Cetus. "Even if Holodniy conceived and reduced to practice after departing Cetus, ... his research was directly related to the collaboration with Cetus." *Id.* at 15a.

In adopting this view, the court below expressly rejected the district court's holding that the Bayh-Dole Act negated Dr. Holodniy's assignment to Cetus because it empowered Stanford to take complete title to the inventions. The Federal Circuit concluded that the "statutory scheme did not automatically void the patent rights that Cetus received from Holodniy," and therefore Cetus (and now Roche) had co-ownership of the patents by virtue of the VCA. Pet. App. 21a.

Finally, because standing principles preclude a patent suit by one co-owner without all other co-owners' agreement and participation, the Federal Circuit determined that Stanford did not have standing, reversed the ownership decision, and vacated the obviousness holding. Pet. App. 27a-28a.

Stanford timely petitioned for *certiorari*, which this Court granted after inviting the views of the Solicitor General.

SUMMARY OF ARGUMENT

The right of a federally funded research institution to retain title to a subject invention under the Bayh-Dole Act derives from the Government's pre-eminent interest in, and right to claim outright, the fruits of its research expenditures. Thus, the institution's right to title does not depend on securing an assignment from the inventor.

Congress enacted the Act following decades during which Government-owned patents had gone largely unlicensed and undeveloped. To rectify this situation, the Act sought to "promote the utilization" and "commercialization" of Government-funded inventions by allowing research institutions such as Stanford that produce inventions with federal funding to retain title to those inventions. The statute was made applicable to all Government agencies and took precedence over existing statutes vesting in the Government title to funded inventions.

This case presents the question whether the title that a contractor is allowed to retain under the Bayh-Dole Act depends upon the contractor also securing effective assignments of rights from its inventors, so that title may be compromised by an inventor's perhaps unknown assignment of his rights to a third party. The statute's text, express purposes, legislative history, and regulations all confirm that the answer to that question is no.

The Act altered the default ownership of a federally funded patent as between the Government and the research institution. It did not make the ownership of either subordinate to rights of the inventor. The Act provides that a federally funded contractor may "retain title" to all "subject inventions"—those "conceived or first actually reduced to practice in the performance of work done under a funding agreement." 35 U.S.C. § 201(e). To retain title, the contractor must satisfy a number of requirements, including, critically, actively pursuing the invention's commercial development. *Id.* § 202(c)(5). If the contractor's efforts fall short in some respect, the Government itself "may receive

title." *Id.* § 202(c)(1)-(3). If the goal of commercial development is not realized, the funding agency retains the power to "march-in"—that is, to intervene and pursue the development of the invention. *Id.* § 203.

The Act's provisions concerning inventors of a subject invention are markedly different. Where a contractor elects to retain title, the contractor must "share royalties with the inventor." *Id.* § 202(c)(7)(B). Where the contractor does not so elect, "the Federal agency may consider ... requests for retention of rights by the inventor subject to" the Act's provisions and regulations. *Id.* § 202(d). These distinctly subordinate rights of the inventor are incompatible with the decision below, holding that the inventor's rights precede and ultimately may, as here, defeat the contractor's statutory right to receive title that the Government itself had usually held in the past.

The legislative history and implementing regulations confirm that the title retained by the research institution rests on the Government's pre-eminent interest based on its provision of funding, which most often in the past had resulted in outright Government ownership. Rather than the institution receiving title by an assignment from the inventor, Congress relinquished the Government's own primary claim of title. It did this to encourage the involvement of private parties, with the goal of increasing the commercial development of Government funded inventions. The statute thus adopted a presumption that ownership of all patent rights in Government funded research will vest in any contractor, who must then comply with explicit

statutory requirements aimed at achieving the Act's purposes.

The implementing regulations have consistently echoed this purpose of the Act, using much of the same terminology, and require, *inter alia,* that funding agreements provide that the contractor may retain the entire right, title and interest throughout the world to each subject invention.

The Federal Circuit's decision is contrary to these authorities. If the contractor's title is only as good as the assignments it has received from its inventors, then title, as here, may always be called into doubt on the ground that an inventor may have made a prior assignment that could remain undisclosed for many years. This uncertainty, and the costs of seeking to uncover possible assignments, would substantially impede the commercialization that is the central objective of the Act. The uncertainty would also impede effective collaboration between commercial entities and federally funded research institutions. The contractual arrangements necessary to define the respective rights of the collaborating parties would be more, not less, difficult if the Federal Circuit's ruling were upheld.

The Federal Circuit's approach also undermines the integrity of the Government's own interest in federally funded inventions. If the contractor's title turned ultimately on the soundness of the assignment that it receives from the inventors, the Government's ability to itself take back title, as the statute under certain circumstances allows, would be severely compromised. So would the Government's ability to march-in and compel the contractor to

license, in order to advance commercial development, since the contractor's shared or uncertain ownership may not be of much commercial interest.

Finally, it is difficult to see how an inventor's co-ownership interest, arising outside of the provisions of the Act, could reasonably be subjected to the statutory conditions and requirements that are imposed by the funding agreement itself. Thus the achievement of the statute's stated goals demands a reading of the statute that recognizes the clear title of contractors who have elected to retain title and comply with the provisions of the Act.

It is also notable that this case implicates uniquely federal interests that reinforce the incorrectness of the decision below. The Bayh-Dole Act directly concerns the construction of United States Government research funding contracts, and their effectiveness in promoting public use of resulting inventions. The focus of those contracts is the determination of rights arising under patents, which subject is likewise one where state law must yield to the commandments of federal law. On the record here, including the fact that the claimed assignment was made after federal research funding had commenced, and respondent's sixteen-year delay in bringing the claimed assignment to light, equitable application of the law requires rejection of respondent's ownership claim, whatever precise construction one places on the Bayh-Dole Act.

ARGUMENT

I. THE BAYH-DOLE ACT GIVES TITLE TO CONTRACTORS LIKE STANFORD WITHOUT REGARD TO ASSIGNMENTS MADE BY INDIVIDUAL INVENTORS

Prior to the Bayh-Dole Act, through numerous vesting statutes, the Government conditioned federal funding on Government ownership of inventions produced as a result of such funding.[9] In the Bayh-Dole Act, Congress instead declared categorically that nonprofit and small-business grantees would step into the Government's shoes as owners of federally funded inventions, provided they follow certain procedures and subject to certain rights retained by the Government. In other words, a federal contractor who complies with the Act is allowed to "retain title" instead of having it go to the Government, and the contractor has the same title that the Government would have had in that event. Such title is not called into question by the action of a federally funded inventor who attempts to assign away title to another.

A. The Text and Structure of the Bayh-Dole Act Demonstrate That the Act Confers Clear Title to Inventions Directly Upon Funded Research Institutions

Against the backdrop of the many agency-specific statutes vesting title to federally funded inventions in the United States and the range of practices at

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[9] Such vesting statutes are still on the books, though they were expressly made subordinate to the provisions of the Bayh-Dole Act by § 210, which states that Bayh-Dole will take precedence over other statutes, including those enumerated there.

other agencies recognizing ownership interests in some private entities, *see supra* at 2-10, Congress enacted the Bayh-Dole Act in 1980 to provide a uniform set of rules for the "[d]isposition" of "Patent Rights in Inventions Made With Federal Assistance." 35 U.S.C. ch. 18; § 202.

As this Court has consistently recognized, Congress has broad authority over intellectual property matters, and its actions in this realm are reviewed for "rational exercise," with "substantial[]" deference to Congress's judgment. *Eldred v. Ashcroft*, 537 U.S. 186, 204-05 (2003). In addition, the Spending Clause permits Congress to impose conditions on recipients of federal funds. *See United States v. Am. Library Ass'n*, 539 U.S. 194, 203 (2003) ("Congress has wide latitude to attach conditions to the receipt of federal assistance in order to further its policy objectives."). Finally, Congress has the authority, "without limitation," to dispose of public property in the "public interest." *United States v. California*, 332 U.S. 19, 27 (1947); *Ashwander v. TVA*, 297 U.S. 288, 338 (1936).

In the Bayh-Dole Act, in order to "promote the utilization" and "commercialization" of Government-funded inventions, Congress expressly established that when inventions "aris[e] from federally supported research or development," 35 U.S.C. § 200, the funded nonprofit institutions and small businesses may secure title in those inventions by complying with statutory procedures and requirements. There is no question in this case that the inventions at issue fall within the scope of the Act, or that Stanford, a qualified grantee, satisfied all the prescribed requirements to secure title.

1. The Act's operative provisions apply to "any subject invention," *id.* §§ 202(a), 203(a), 204, a term that the Act defines as "any invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement." *Id.* § 201(e). Since an institution can only create an invention through the actions of its employees, this language is naturally read to include[10] all inventions made by the contractor's employees with the aid of federal funding.[11] Also, the definition of "funding agreement" makes clear that the Act applies where the "research work is funded in whole or in part by the Federal Government," *id.* § 201(b), so the quantity of federal funding is not dispositive. Thus inventions made by the contractor's employees after the commencement of any federal funding are "subject inventions" covered by the Act, whether or not the individual inventors have expressly conveyed their rights in the invention to the contracting institution.

Here, the invention claimed by the patents-in-suit is clearly a "subject invention." It was both

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[10] This definition is not exhaustive. For example, an invention could also be "of the contractor" and covered by the Act where the institution has purchased the concept of an invention from an unfunded, non-employee inventor, and later actually reduces it to practice with the aid of federal funding.

[11] For an employee of the contractor to be an inventor, he or she must play some role in the conception of the invention. *E.g.*, *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460-61 (Fed. Cir. 1998). The statute's limitation to "invention[s] of the contractor" thus excludes from the Act's coverage inventions created by third parties without assistance of federal funding, where the contractor's employees had no role in its conception.

conceived *and* reduced to practice with the aid of federal funding that was in place no later than 1988, before Dr. Holodniy began visiting Cetus in 1989. *See supra* at 17.[12] And it was an "invention of the contractor" because the named inventors on the patents-in-suit—all of them—were researchers employed by Stanford. At no point has Cetus or Roche ever disputed inventorship to assert that a non-Stanford-employee was a co-inventor. It is far too late to do so now.[13]

2. Pursuant to the Act's allocation of rights as between the Government, the contractor, and the inventor(s), title to the invention at issue here vested in Stanford. Subject to the Government's ability to provide otherwise in the funding agreement, Section 202(a) states that "[e]ach nonprofit organization or small business firm may, within a reasonable time after disclosure [of the subject invention to the Government], elect to retain title to any subject invention." 35 U.S.C. § 202(a). This right to retain title is conditioned on compliance with precisely

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[12] Clearly, then, Dr. Holodniy's execution of the VCA, on which Respondent's purported ownership interest depends, occurred while the project he was working on at Stanford and Cetus was already receiving NIH funding that triggered application of the Act. *See* JA 95, 136. Such a prospective assignment by a researcher of the fruits of on-going, federally funded research obviously cannot stand, given Bayh-Dole's express provisions defining a different disposition of any resulting inventions.

[13] In addition, in ruling that Roche was a co-owner of the patents-in-suit, the Federal Circuit rested on the express assumption that Dr. "Holodniy [both] conceived and reduced to practice after departing Cetus"—an assumption contrary to any inventorship by Cetus. Pet. App. 15a; *see also* Pet. App. 102a-104a.

defined procedural requirements that seek to protect the Government's interests and, in the case of non-compliance, allow the Government in its discretion to "receive title" to the invention.

Stanford took all the steps required by the Act. First, Stanford made the required timely disclosure of the subject invention to the funding agency, without which "the Federal Government may receive title." *Id.* § 202(c)(1). *See* Pet. App. 5a-6a. Stanford also made the required timely written election to retain title, *id.* § 202(c)(2), and filed timely patent applications, *id.* § 202(c)(3), absent either of which the Government is likewise empowered to "receive title." *See* Pet. App. 5a-6a. Nor has any suggestion been made that Stanford has failed to honor any other requirements of the Act. *See supra* at 13-15.

By its terms, the Act sets out certain requirements for a contractor to secure "title" under the Act. Its omission of other prerequisites supports a strong inference that Congress did not intend to require contractors to take other steps—such as acquiring title to the invention from the contractor's employees—before being entitled to retain title. This routine application of the principle of *expressio unius est exclusio alterius*, *TRW Inc. v. Andrews*, 534 U.S. 19, 28-29 (2001), means that Stanford's title to the patents-in-suit should not be called into question where it has satisfied all the statutory prerequisites to securing title, on the ground that it failed to take other steps that are nowhere discussed there.

3. The relationship of Bayh-Dole to the previous regime that governed federally funded inventions confirms that it confers title upon funded contractors

that is not qualified or limited by competing ownership rights of inventor employees engaged in the funded research. Before the enactment of Bayh-Dole, numerous vesting statutes automatically vested title to federally funded inventions *in the Government*, irrespective of any agreements concerning title between the federal contractor and the individual inventor. *See, e.g.*, 42 U.S.C. § 2182 ("[a]ny invention ... made or conceived in the course of or under any contract [with the Atomic Energy Commission] ... shall be vested in, and be the property of, the Commission"); 42 U.S.C. § 2457 ("[w]henever any invention is made in the performance of any work under any contract of the [National Aeronautics and Space] Administration ... such invention shall be the exclusive property of the United States"); 42 U.S.C. § 5908(a) ("[w]henever any invention is made or conceived in the course of or under any contract of the Department [of Energy] ... title to such invention shall vest in the United States").

The Bayh-Dole Act expressly displaced these earlier statutes, stating that its provisions addressing "[d]isposition of rights," would henceforth "take precedence" over each of them. 35 U.S.C. § 210(a). Given the established practice of taking Government title to most federally funded inventions, it was natural to describe the change effectuated in the Bayh-Dole Act as allowing the contractor "to retain title." § 202(a). Based on this prior history, the most reasonable understanding of the statute's language is that it allows a contractor to "retain title," as contrasted with having title vest or be taken entirely by the Government.

4. Separate provisions of the Act use the words "acquire" and "receive" as interchangeable with the word "retain" in § 202(a), thus confirming that the Act vests new title in the contractor and does not simply confirm title that the contractor previously acquired from someone else (such as the inventor). For example, in setting forth the circumstances under which the Government may compel a contractor to license a federally funded invention, § 203 states that the Government shall have such "march-in" rights "[w]ith respect to any subject invention in which a small business firm or nonprofit organization *has acquired title under this chapter*." 35 U.S.C. § 203(a) (emphasis added). But § 202(a) is the *only* provision "under this chapter" (chapter 18) that specifies when a small business firm or nonprofit organization will have title to a subject invention. Thus, § 203(a) unambiguously recognizes that, in exercising its right to "retain" title under § 202(a), a contracting institution is "acquir[ing]" title—not merely holding onto preexisting title.

Similarly, § 204 refers to small business firms and nonprofit organizations that "receive[]" title to any subject invention. This provision likewise recognizes that § 202(a) operates as an affirmative grant of title to the contracting institution, and not simply as a confirmation of whatever title is already acquired through other means.

5. The Act's provisions expressly allowing title to the subject invention to vest in the inventor under certain specified conditions further confirm that § 202(a)'s conferral of rights on the contractor is not subject to any pre-existing rights of, or transfers from, the inventor. Section 202(d) provides that "[i]f

a contractor does not elect to retain title to a subject invention," the Government may "consider and after consultation with the contractor grant requests for retention of rights by the inventor, subject to the provisions of this Act and regulations promulgated hereunder."

If, as Respondents would have it, the inventor's rights in "subject inventions" under Bayh-Dole took precedence, such that the contractor gets only what the inventor has given it, then this provision recognizing a subordinated and hedged possibility of the inventor receiving title would make no sense. By contrast, if "retain" is read as a synonym for "acquire" or "receive," then § 202(d) makes perfect sense. The inventor's opportunity to take title is only a contingent possibility, and it does not exist unless the institutional contractor fails to retain title and the Government itself declines to "receive title."

The position of the inventor is further illuminated by § 202(c)(7)(B), which requires a nonprofit organization that elects title to a subject invention to "share royalties" with the inventor.[14] There would be little reason to confer such a statutory entitlement upon the inventor, if the premise of the statute were that the inventor already owns the patent until such time as he or she assigns it to someone else. The provision makes sense, by

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[14] Thus, it is probably not correct to say that an inventor working on federally funded research has no ability to assign away any rights in connection with it. Since the statute itself gives a right to royalties in future inventions to the inventors, § 202(c)(7)(B), perhaps an assignment of that right—specifically provided for by the statute—would be permissible.

contrast, when seen as an assurance of reasonable royalty payments to an inventor whose ownership rights in the patent were supplanted by the express terms of the statute, based on the pre-eminent federal interest that arises as a result of federal research funding.

B. The History of the Bayh-Dole Act Reveals a Purpose to Promote Commercialization by Transferring to Research Institutions the Government's Right to Own Federally Funded Inventions

H.R. 6933, the bill that ultimately became the Bayh-Dole Act, was introduced on March 26, 1980, and contained in section six a new chapter of the Patent Code, Title 35, addressing the "Government Patent Policy." *Id.* This bill, which tracked the structure and many of the provisions of the present Act, passed the House on November 17, 1980, and the Senate began debating it three days later. 126 Cong. Rec. 29,901 (1980); *id.* at 30,360.

In the Senate, certain language of the House bill was immediately altered by an amendment proposed by Senators Bayh and Dole "in the nature of a substitute." *Id.* at 30,361 (Sen. Dole). Earlier in the year, the Senate had overwhelmingly passed a parallel bill, S. 414. *See id.* at 8746. When that bill was offered in the House as H.R. 2414, it failed to move forward, and the House instead acted on its own H.R. 6933. The Bayh-Dole substitute Amendment 1779 struck out section six of H.R. 6933 and replaced it with "the patent policy incorporated in S. 414." *Id.* at 30,364 (Sen. Bayh).

While the original language of H.R. 6933 had stated that "[a] contractor that is a small business or a nonprofit organization *will acquire* title to its contract invention," *see id.* at 29,891 (§ 383(a)) (emphasis added), the Senate bill allowed "[e]ach nonprofit organization or small business firm" to "*elect to retain* title to any subject invention." *Id.* at 30,361 (§ 202(a)) (emphasis added).

The earlier Senate debates on S. 414, which included discussion of this latter language, indicate that this "[d]isposition of rights" was understood as "granting to the universities and small companies the right of first refusal for patents arising from their Federal grants or contracts." *Id.* at 2007 (Sen. Weicker); *see id.* at 1991 (Sen. Dole). The debate made clear that the Government would "relinquish patent rights that would encourage and stimulate private industry to develop discoveries into products available to the public." 126 Cong. Rec. 1796 (1980) (Sen. Bayh); *see also id.* at 1798 (Sen. Matthias) ("[o]ur bill would encourage the Federal Government to grant patent rights").

No Senator in favor of S. 414 suggested that an assignment from the inventor was necessary for universities and small businesses to "retain" patent rights. To the contrary, statements from several Senators all confirm that "retain," as used in § 202(a) of S. 414, is synonymous with "obtain," *i.e.*, that "retain" was not used to suggest that some third party had a pre-existing right in the invention. *Id.* at 1796, 1798, 1799, 1991, 2002 (Sens. Bayh, Matthias, Kennedy, Dole, and Chafee).

Senate Judiciary Committee Report Number 96-480 contains "[t]he full legislative history" of S. 414. 126 Cong. Rec. 30,364 (1980) (Sen. Bayh). This Report indicates that the bill's provisions, like H.R. 6933, were "designed to promote the utilization and commercialization of inventions made with Government support" and remedy the economic stagnation and crisis in innovation that the United States was experiencing. S. Rep. No. 96-480, at 1-3 (1979). These objectives were to be accomplished by "automatically grant[ing] small businesses and nonprofits title to inventions arising from Government-supported research." *Id.* at 36.[15]

Following the Senate's passage of H.R. 6933, as amended in the Senate, the House took up and passed the amended bill. 126 Cong. Rec. 30,556-60 (1980).[16] In signing the Act into law, President

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[15] The meaning of the Act as ultimately passed is further illuminated by the House Report. In commenting on the slightly different language in the original House bill, the House Report noted that it "establishe[d] a presumption that ownership of all patent rights in government funded research will vest in any contractor who is a non-profit research institution or a small business." H.R. Rep. No. 96-1307, pt. 1, at 5 (1980), *reprinted in* 1980 U.S.C.C.A.N. at 6464. While the "will acquire" language of the original House passed version of H.R. 6933 differed slightly from that of S. 414, there is no indication that any legislator viewed the differences as significant or altering the substance of the legislation. Indeed, following the Senate's substitution of "elect to retain" for "will acquire," the sponsor of H.R. 6933, Representative Kastenmeier, stated that the Senate had left "intact" the provisions "relating to small businesses and universities." 126 Cong. Rec. 30,560 (1980).

[16] The primary objection raised to the bills in either the House or Senate was that they gave away too much of the Government's rights, not that they interfered too much with the

Carter confirmed that the Act "enables small businesses and nonprofit organizations to *obtain* title to inventions made with Federal support." Statement on Signing H.R. 6933 Into Law, 16 Weekly Com. Pres. Doc. 2803, 2804 (Dec. 12, 1980) (emphasis added).

After the enactment of Bayh-Dole, the Comptroller General's first annual report confirmed that "Section 6 establishes a uniform policy for assigning title to inventions made by small business or nonprofit contractors during Government-sponsored research." Comptroller Gen., *Patent and*

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rights of inventors. *See, e.g.*, H.R. Rep. No. 96-1307, pt. 1, at 29 (1980), *reprinted in* 1980 U.S.C.C.A.N. at 6487 (dissenting views of Rep. Jack Brooks) ("The major problem I have with H.R. 6933 is that it violates a basic provision of the unwritten contract between the citizens of this country and their Government; namely that what the Government acquires through the expenditure of its citizens' taxes, the Government owns."); 126 Cong. Rec. 2002 (1980) (Sen. Long) ("When the public has paid for the research, the public is entitled to the benefit of it.").

Sponsors of the legislation responded by noting that the public would not obtain any benefits absent the grant of title to contactors. *See, e.g.*, 126 Cong. Rec. 8739 (1980) (Sen. Dole) ("The incentive provision for private industry for the development of inventions, is designed to insure that the American public gets a return on the investment that has been made in research."); *id.* (Sen. Bayh) ("But as long as that patent is not developed and made available in the marketplace, the public is receiving no benefits for the research money that has been expended in support of the invention."); *id.* at 29,898 (Rep. Fuqua) ("I am aware of the criticism that granting contractors exclusive rights to Government-funded inventions enriches contractors at the expense of the taxpayer. However, I believe that without the grant of exclusive rights, virtually no economic benefits which would flow from commercialization would be realized.").

Trademark Amendments of 1980 Set the Stage for Uniform Patent Practice by Federal Agencies (PAD-82-32) 1 (1982).

C. The Implementing Regulations Confirm Stanford's Reading of the Act

Bayh-Dole's implementing regulations, originally issued by the Office of Federal Procurement Policy[17] and entitled to *Chevron* deference, confirm that Bayh-Dole "coupled" the Government's "large investment" in research with "the incentive of invention *ownership* in small businesses, non-profits and universities" for the purpose of "initiat[ing] a significant increase in the commercialization of inventions resulting from these programs." *See* Patents; Small Firms and Non-Profit Organizations, 46 Fed. Reg. 34,776, 34,776, ¶ 3 (July 2, 1981) (emphasis added).

The subsequently issued permanent regulations in Circular A-124 likewise clarify Bayh-Dole's disposition of rights. "This Act *gives* nonprofit organizations and small businesses, with limited exceptions, *a first right* of refusal *to title* in inventions they have made in performance of Government grants and contracts." Patents—Small Firms and Non-Profit Organizations, 47 Fed. Reg. 7556, 7559, ¶ 4 (Feb. 19, 1982) (emphases added); *cf.* 126 Cong. Rec. 2007 (1980) (Sen. Weicker). Thus, the agency charged with implementing Bayh-Dole

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[17] *See* 35 U.S.C. § 206 (1982), *amended* Pub. L. 98-620, § 501(10), 98 Stat. 3335, 3367 (1984).

interpreted § 202(a) as giving the contractor, and not the inventor, the first right to title.[18]

The current regulations, which were issued by the Department of Commerce after Public Law No. 98-620 transferred regulatory authority from the Office of Federal Procurement Policy in 1984, maintain this interpretation. Indeed, the bulk of the current regulations track, word-for-word, Circular A-124. *Compare, e.g.*, 37 C.F.R. § 401.1(a) (2010) *with, e.g.*, 47 Fed. Reg. at 7557. Two provisions of the current regulations are especially relevant in this case.

First, the regulations provide that "[t]he *Contractor* may retain the *entire* right, title, and interest throughout the world to each subject invention." 37 C.F.R. § 401.14(a)(1), ¶ (b) (second emphasis added). Such a statement cannot be squared with a view that Bayh-Dole only determines the disposition of rights between the Government and the institution, and leaves the inventor with primary rights, yet to be addressed.

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[18] Circular A-124 also addressed Bayh-Dole's applicability to collaborative research projects. 47 Fed. Reg. at 7557. The Act applies to cooperative projects "expediting or more comprehensively accomplishing the research objectives of the Government sponsored project." *Id.* It does not apply, however, to inventions that are "related but separate" from the federally funded research. *Id.* The Circular gave an example of such closely related but separate projects: where one has "research objectives to expand scientific understanding in [a] field" and the second has "as its objectives the application of such new knowledge to develop usable new technology," only the federally funded project is subject to Bayh-Dole. *Id.*

Second, contrary to any claim that Dr. Holodniy's use of Cetus's information and equipment entitled it to certain rights, § 401.1(a)(1) indicates that "the use of new fundamental knowledge from one [project] in the performance of the other [is] not [an] important determinant[] [of Bayh-Dole's applicability,] since most inventions rest on a knowledge base built up by numerous independent research efforts extending over many years." The fact that Dr. Holodniy may have obtained a better understanding of the then-publicly-known PCR technique from conducting some of his work at Cetus in no way suggests that Bayh-Dole does not apply to the resulting inventions. What matters is that the research by Dr. Holodniy and others, at Stanford and at Cetus, from 1988 on, was pursued with the help of grant money from NIH.

Not only do these regulations confirm the plain-text reading of the statute, but they are also entitled to deference to the extent that the text admits of any ambiguity. *See Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 843-44 (1984); *cf. Whitman v. Am. Trucking Ass'ns*, 531 U.S. 457, 477-82 (2001). The regulations, which link the grant of title to the contractor to the express purpose of achieving commercialization, have remained consistent for thirty years, thus "reflect[ing]" the agencies' "considered views." *See Long Island Care at Home, Ltd. v. Coke*, 551 U.S. 158, 171 (2007). These settled views are certainly not arbitrary. Rather they reflect the most reasonable interpretation of the text, history, and purposes of Bayh-Dole as detailed above, and have stood without challenge for nearly three decades.

D. The Federal Circuit's Construction of Bayh-Dole Undermines the Act's Express Purposes

1. Vesting title in contracting institutions is necessary in order to maximize commercial utilization of inventions resulting from federally funded research. In enacting the Bayh-Dole Act, Congress included within the statute itself a clear indication of the Act's purpose: "to use the patent system to promote the utilization of inventions arising from federally supported research." 35 U.S.C. § 200. To implement that statutory purpose, the Act "gives nonprofit organizations and small businesses ... a first right of refusal to title." 47 Fed. Reg. at 7559, ¶ 4. Congress recognized that giving such contractors clear title was necessary to spur the additional investment required to turn the initial invention into a commercially viable product. 125 Cong. Rec. 1796-98 (1980) (Sen. Bayh).

Congress's decision was a wise one. Since Bayh-Dole's passage, "American universities have witnessed a tenfold increase in the patents they generate, spun off more than 2,200 firms to exploit research done in their labs, created 260,000 jobs in the process, and now contribute $40 billion annually to the American economy." *Innovation's Golden Goose*, The Economist, Dec. 14, 2002, at 3.

The Federal Circuit's decision in this case not only ignores the language and structure of the Act, but also ignores the statute's thirty-year period of consistent and successful application, and threatens this success by fundamentally undermining Bayh-Dole's framework. In contrast, giving primacy to § 202's explicit "[d]isposition of rights" provides

certainty that is essential if Bayh-Dole's developmental purpose is to continue to be fulfilled.

Under the decision below, even when a university or small business elects to retain title and complies with all of the requirements of the Bayh-Dole Act, it can never be sure that it has obtained clear title. Instead, title will remain clouded by the potential that an inventor, at some point, may have inadvertently or intentionally entered into an undisclosed agreement with an unknown third party years before a patent even issued. Such an unknown prior assignment by a named inventor may deny the institution any title at all (in the case of a single inventor) or may mean that the institution shares ownership with others, if some but not all co-inventors have assigned rights away. In the latter case, as here, the purported assignee of such rights can preclude the university and the other inventors from obtaining any royalties at all, prevent licensing to other parties, and thus stand in the way of the realization of the fruits of federal funding.

Such "uncertainties" create "artificial restraints" on the commercialization of inventions by inhibiting the additional investments necessary to reduce the invention to a commercially viable product. S. Rep. No. 96-480, at 19 (1979). Substantial investments must be made to convert a patented invention to a marketable commercial product, and the willingness of prudent investors to make such investments is greatly impaired when there is doubt about the nature of the rights that are being secured by a patent license.

Especially in the biotechnology area, where testing and governmental approvals are often enormously expensive and accompanied by long periods of delay, uncertainty about a patent holder's ability to convey an exclusive license can pose a major obstacle to successful commercial development of the innovation. *See* 126 Cong. Rec. 2007 (1980) (Sen. Weicker) ("A new drug, for example, frequently requires careful testing on laboratory animals. If successful, years of carefully controlled clinical trials will follow.... It is clear that a drug manufacturer will invest the time and money to bring the product to the marketplace only if there is a reasonable certainty that the investment will be recovered through sales.").

It is no answer to suggest that a contractor like Stanford can alleviate such uncertainties by combing through the files of each faculty member, graduate student, or employee who may be an inventor and seeking documents from all of the third parties with whom those people may have interacted. Even such due diligence cannot prove a negative. Absolute assurance that a contrary assignment does not exist is impossible. And performing such a wide-ranging inquiry on each "subject invention" would significantly increase the university's administrative costs, thus undermining Bayh-Dole's correlative objective of "minimiz[ing] the costs of administering policies in this area." 35 U.S.C. § 200.

By contrast, giving primacy to § 202's "[d]isposition of rights" avoids the need for a costly and wide-ranging due diligence inquiry, thus reducing administrative costs for universities. 35 U.S.C. § 200. It also "promote[s] the utilization of

inventions" by providing the clear title that is most likely to call forth the substantial additional investment usually required to turn the invention into a commercially viable product. *Id.*

2. The Federal Circuit's ruling also undermines the Government's significant interests in seeing that the research it funds serves the public interest. The statute's first section states, as another central congressional objective, "ensur[ing] that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions." 35 U.S.C. § 200. But, as the Solicitor General stated, the decision below "jeopardize[s]" the Government's rights that are explicitly secured to it under the Act. CVSG Br. at 18.

The provisions that confer title upon contractors, subject to numerous statutory conditions, also empower the Government, upon failure of a number of those conditions, to itself "receive title" and/or "march-in" and confer rights upon another. §§ 202(c)(1), (2), (3), 203. If the contractor's rights were only the contingent set recognized by the Federal Circuit, then the Government's rights would be diminished as well. This would compromise the Government's ability to protect the public interest and to take back clear title for itself. A university that does not obtain clear title cannot "convey to the Federal agency, upon written request, title to any subject invention," even though such a conveyance may be required under Bayh-Dole and its implementing regulations. 37 C.F.R. § 401.14(a), ¶ d.

The Federal Circuit sought to avoid the consequences of its position by suggesting that, where the contracting institution does not already have title to an invention, the Act might nevertheless provide the Government with "a discretionary option to [the inventor's] rights." Pet. App. 18a-19a. But that illusory hope finds no support in the statute, and the Federal Circuit pointed to none. The Act provides that the title of the contractor reverts back to the Government when conditions triggering that result arise, § 202(c)(1), (2), (3), and thus the only "title" that the Government "may receive" is the same "title" that the contractor received pursuant to its election under § 202(a). Clear title cannot revert back if it did not exist in the first place.[19]

Similarly, the Government's ability to exercise "march-in" rights in response to the contractor's failure to achieve utilization of a subject invention can logically pertain only to the rights that the contractor in fact possessed. If an inventor's earlier unauthorized assignment really is effective to confer a right to shared ownership in a federally funded patent, that assignee ownership interest would be beyond the reach of the Government when it later

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[19] Consider the hypothetical scenario in which, under the Federal Circuit's reasoning, another university that received only partial title due to an earlier assignment by an inventor to Company A were to breach one of the conditions of § 202(c)(1)-(3), causing the Government to intercede and receive title. It is hard to imagine that the property rights of Company A, declared by the court below to be good as against that university and other third parties, could be voided at some future time based on governmental intervention due to the university's perceived breach of its obligations under Bayh-Dole.

"marches in" because of the contractor's failure to achieve commercial development. A contrary conclusion would amount to creating a bizarre type of assignee "ownership" that the Government is free to rescind, not due to any breach of duty by the assignee, but through a failing by another—here the contractor.

The language in the Bayh-Dole Act does not remotely suggest any such strange innovation. Nor does it contemplate a "march-in" process in which the Government's pre-eminent interest in funded research may be rendered an impotent nullity, by an inventor's quiet assignment of his rights. Straightforward application of the statute's language defining the "[d]isposition of rights" in "subject inventions" avoids both of these problems.

3. The decision below diminishes the federal interest in funded research in another respect as well. It creates a huge loophole in Bayh-Dole's statutorily created obligations with respect to inventions produced with federal funds. Undisclosed assignment agreements like that executed by Dr. Holodniy at Cetus are quite unlikely to embody any of the obligations that Bayh-Dole imposes with respect to a "subject invention." These include reporting the invention to the Government, granting the Government a license, manufacturing the invention in the United States where practicable,[20] or

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[20] *See* 35 U.S.C. § 204. Although Respondent happens to manufacture its products in the United States (Resp. Supp. Opp. 12), that mere fortuity is not required by the VCA. Under the Federal Circuit's decision, Respondent, which is itself affiliated with a Swiss parent company, appears to be free at any time to move manufacturing to a foreign location.

granting the Government march-in rights. And this is true, notwithstanding that the statute and regulations expressly impose such obligations on inventors, where they receive title with agency permission, subject to an express procedure outlined in the Act. 35 U.S.C. §§ 202(d), 204; 37 C.F.R. § 401.9.

Thus, in this way as well, by allowing the Cetus VCA form to take precedence, rather than focusing on the statutory "[d]isposition of rights" in § 202, the Federal Circuit's decision "calls into question the Government's ability to manage federally funded inventions for the benefit of the public." CVSG Br. at 18.

4. Honoring Stanford's right of first refusal in the inventions also best advances Bayh-Dole's purpose of "promot[ing] collaboration between commercial concerns and nonprofit organizations." 35 U.S.C. § 200. Bayh-Dole provides a clear rule that federal contractors like Stanford can obtain full patent rights in subject inventions without regard to any unilateral acts by individual inventors. History, both leading up to the Bayh-Dole Act and in the thirty years since, teaches that collaborations both in innovation and in commercial development of Government-funded inventions, are best encouraged by this sort of clear rule about how ownership rights can be acquired and what those rights are. The Federal Circuit's rule would undermine such collaboration.

Bayh-Dole expressly seeks "to promote collaboration between commercial concerns and nonprofit organizations, including universities." 35

U.S.C. § 200. This policy reflects a clear intention that the entire process contemplated by the Act, involving both innovation and commercial development of resulting inventions, is to take place within the context of the free enterprise system, and to involve effective collaboration between the research institutions and private businesses. *See* 126 Cong. Rec. 1799 (1980) (Sen. Kennedy) ("[i]f [small businesses and universities] are able to obtain patent rights to inventions, they will be in much better positions to secure the venture capital necessary to reduce the inventions to commercial use"); *see also id.* at 1796, 2002, 8739 (Sens. Bayh, Chaffee, and Dole).

Collaborations, in the areas of pure and applied research, and also in product development, are extremely widespread today, and are almost universally governed by contractual understandings between the parties. *See* Erin Shinneman, Note, *Owning Global Knowledge: The Rise of Open Innovation and the Future of Patent Law*, 35 Brooklyn J. Int'l L. 935, 954-55 (2010). Such projects will carry not only a range of duties, but also a variety of definable and undefinable risks. Effective collaboration demands both trust and confidence in the ability to accomplish useful targeted ends, and assessment and allocation of the attendant risks. Uncertainty in the form of risks that might significantly jeopardize the collective undertaking is thus an obstacle with which collaborators must contend. *Id.*

Prior to Bayh-Dole, the jumble of varied procedures undermined effective collaboration. *See supra* at 9-10. Bayh-Dole, by contrast, established a single clear procedural path by which research

institutions can receive clear and indisputable title, subject to defined duties and specific residual rights in the Government. The Act's relative success in achieving commercial development of funded inventions is in no small part due to its clarity in defining the rights of respective parties.

The Federal Circuit's ruling threatens a return to the bad old days. Allowing a research institution's Bayh-Dole-derived title to be called into question based on an inventor's prospective transfer years earlier will be an impediment to effective collaboration. The complex collaboration agreements now used widely by sophisticated businesses and research institutions can reach a suitable bargain, provided that they have reasonable clarity about their starting place.[21] What will make such bargains much more difficult, where the issue is whether and on what terms to acquire a license for the purpose of product development, is doubt about the nature of the ownership right that the licensor holds. And that is precisely the uncertainty that the decision below creates.

Respondent has argued, to the contrary, that the straightforward construction of the statute's words would "chill innovative collaboration," because a party in Cetus's position would have no effective way to "protect its intellectual property while

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[21] There is little doubt that Cetus and Stanford could have reached such an agreement in 1989, had Cetus simply been forthright in approaching Stanford if it wished some recompense for allowing Dr. Holodniy's use of their facilities in connection with his on-going federally funded research. And there is even less doubt today, when the complexity and sophistication of such arrangements has grown significantly.

collaborating with a university," and thus, presumably, such collaborations would be greatly curtailed. Resp. Supp. Opp. 10, 13. Respondent's contention rests on a mistaken premise about the limits on research institutions' ability to strike agreements defining the terms of collaboration.

The Act's "prohibition upon the assignment of rights to a subject invention in the United States without the approval of the Federal agency," § 202(c)(7)(A), only requires such consent with regard to an assignment to another of *full* title to a subject invention. Funded research institutions may, and frequently do, strike a variety of less categorical bargains to foster such collaboration. In fact, the very funding agency involved in this case, the NIH, has guidelines specifically permitting agreements that provide industrial collaborators with "preferential access and/or rights to intellectual property deriving from [funding] Recipient research results," including agreements giving industrial collaborators a first option to become the university's exclusive licensee for commercial development. *See* Developing Sponsored Research Agreements: Considerations for Recipients of NIH Research Grants and Contracts, 59 Fed. Reg. 55,673, 55,675-76 (Nov. 8, 1994).[22]

In short, clarity and certainty are the touchstones of successful collaboration because industry

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[22] On this point, the difference between an assignment, which transfers substantially all of the patent rights, and a license, which does not, becomes telling. *See AsymmetRx, Inc. v. Biocare Med., LLC*, 582 F.3d 1314, 1319-21 (Fed. Cir. 2009) (discussing the difference between an assignment and a license).

collaborators can contract around rights that are clearly defined. Adhering to the statute's "[d]isposition of rights" in "subject inventions" produces that clarity and certainty. Respondent's interpretation, by contrast, clouds title to such "subject inventions" and diminishes the prospects for collaboration as a result.

II. THE UNIQUE FEDERAL INTERESTS AT STAKE IN THIS CASE PROVIDE ADDITIONAL REASONS TO REVERSE THE DECISION BELOW

The conclusion that Stanford's rights in the patents in suit cannot depend on the vagaries of private contract law is strengthened because of the "uniquely federal interests at stake" in this case. *Boyle v. United Techs. Corp.*, 487 U.S. 500, 504 (1988). As in *Boyle*, cases arising under the Bayh-Dole Act "border[] upon two areas that [this Court] has found to involve such uniquely federal interests:" determination of rights under federal contracts and patent law. *Id.* (internal quotation marks omitted).

Bayh-Dole's express directives about ownership of inventions produced with federal funding means that this case differs materially from the mine run of patent cases, where determination of patent ownership may present questions of state law. *See Jim Arnold Corp. v. Hydrotech Sys., Inc.*, 109 F.3d 1567, 1572-77 (Fed. Cir. 1997) (discussing several decisions of this Court). Where "uniquely federal interests" are involved, otherwise applicable rules of state law may be "pre-empted and replaced, where necessary, by federal law of a content prescribed (absent explicit statutory directive) by the courts—so

called 'federal common law" *See Boyle*, 487 U.S. at 504 (1988) (internal quotation marks omitted).

Like *Boyle*, the Act directly involves obligations and rights arising under contracts to which the Government is a party. *Id.* At the same time, the provisions at issue involve rights arising under patents, an area in which "state regulation ... must yield to the extent that it clashes with the balance struck by Congress." *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 152 (1989) (invalidating Florida law protecting unpatented boat design); *see Lear, Inc. v. Adkins*, 395 U.S. 653, 673-74 (1969) (overriding state court enforcement of contractual royalty provisions during the pendency of a challenge to patent); *Brulotte v. Thys Co.*, 379 U.S. 29, 32 (1964) (overriding state court enforcement of contractual royalty provisions beyond the term of the patents). Given the pre-eminent federal interest in the ownership of patent rights arising from federal funding, including the need for certainty of title, a uniform body of federal law rather than a variety of state-law rules should govern the validity and priority of an employee-inventor's attempts to assign title.

The Federal Circuit recognized that federal common law governs the question of who has title to the patents at issue here. *See* Pet. App. 12a. But it failed to draw the correct lesson from that point. It failed to weigh properly—or at all—the nature of the federal interest arising from governmental expenditure of billions of dollars of taxpayer funds to promote the public good through research and the commercial realization of resulting inventions.

As reflected in years of practice under the vesting statutes, the Government has an undisputed right to simply claim ownership of inventions developed as a result of federal funding. The decision reflected in the Act, instead to direct title to the funded research institution subject to express conditions, sought among other explicit goals to promote the commercial development of such funded inventions. If research funding is to bear fruit through the realization of that goal, the title that the research institution receives and attempts to license to others must be certain and reliable. Such certainty of title cannot be squared with an open-ended right in the inventor to assign away that ownership interest to some third party, even before it has come into existence.

The Bayh-Dole Act thus can reasonably be viewed as imposing, with regard to inventors working on federally funded research, a status analogous to that recognized by the "hired to invent" doctrine, previously recognized by this Court as a matter of pre-*Erie* general federal common law. This doctrine provides that where an employee is hired for the particular purpose of engaging in inventive activity for his employer, ownership of any inventions developed in the course of employment vests as an original matter in the employer. *See Standard Parts Co. v. Peck*, 264 U.S. 52, 59-60 (1924); *see generally* Catherine L. Fisk, *Removing the 'Fuel of Interest' from the 'Fire of Genius': Law and the Employee-Inventor, 1830-1930*, 65 U. Chi. L. Rev. 1127 (1998). Within the Bayh-Dole scheme, when similar reasoning is applied to employees engaged in federally funded research, it supports the conclusion that the Government's funding gives it ultimate

control over the resulting inventions. This reasoning supplements and supports all the other grounds, discussed above, for refusing to allow frustration of the statute's objectives by purported assignment to third parties of an inventor's claimed interest in those inventions.

Moreover, with regard to patent law—the second area of uniquely federal interest on which this case touches—it is notable that rights arising under the patent laws have always involved equitable considerations.[23] The Federal Circuit, however, failed properly to take these equitable considerations into account when adjudicating title to the patents in this case.

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[23] Under the original Patent Act, 1 Stat. 109, 111 § 4 (1790), the injunctive aspect of the patent right to exclude was secured in state courts through a suit at equity, and in federal courts only under diversity jurisdiction. See 5 Donald A. Chisum, *Chisum on Patents* § 20.02[1][a] (1995). In 1819, Congress conferred general equity jurisdiction over patent cases upon federal trial courts. *Stevens v. Gladding*, 58 U.S. (17 How.) 447, 455 (1855). This grant was expanded by the 1870 Patent Act, which gave federal equity courts the special power in patent cases to award damages. *E.g.*, *Clark v. Wooster*, 119 U.S. 322 (1886). While the current Patent Act, U.S. Code tit. 35, has altered this arrangement to some degree—most notably by eliminating the remedy of accounting, *see* Chisum, *supra*, at § 20.02[4]—equity still plays a large role in patent cases as evidenced by the injunctive remedy and the defenses of inequitable conduct, laches, and estoppel (whether equitable estoppel, assignor estoppel, or estoppel based on the patent prosecution history). *See generally eBay, Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006); Leslie J. Lott, *Equitable Defenses in Patent Infringement Litigation*, 572 P.L.I. Pats., Copyright, Trademarks & Literary Prop. Course Handbook Ser. 1119 (Sept.-Nov. 1999).

In particular, the Federal Circuit paid no heed to equities when it breezed by the facts of this case and concluded that Roche could claim an ownership interest in the patents-in-suit. Roche and Cetus slept on their purported rights for over fifteen years, while Stanford, confident of its ownership because it had fulfilled the statute's requirements, continued to invest time, money, and effort in licensing and commercializing the patents as well as performing further research.

Several other factors raise additional serious questions about the enforceability of the VCA's purportedly very broad assignment of ownership rights on the facts of this case. Enforcement of such a prospective assignment of future rights is itself equitable in nature, *see Pomeroy on Equity Jurisprudence*, § 1288 (stud. ed. 1907), and thus deserves careful scrutiny. *See* Ernest Bainbridge Lipscomb III, 5 *Lipscomb's Walker on Patents* § 19:16 (3d ed. 1986). The Cetus agreement was signed at a time when Dr. Holodniy was already working pursuant to a federal research grant, and had already "agreed to assign" to Stanford any interest flowing from his current work, which during 1989 was pursued both at Stanford and at Cetus. Moreover, while the Cetus agreement was denominated a "confidentiality agreement," the provisions relevant here purporting to assign ownership interests do not require that the accessed, triggering information be confidential in nature. The Federal Circuit decision did not turn on whether the information learned at Cetus was confidential, Dr. Holodniy did not believe that it was, Pet. App. 96a, and that view is borne out by the fact that a detailed article was published in

1991 concerning the work done by Dr. Holodniy at Cetus. JA 135-149.

An interpretation of the Bayh-Dole Act that allows Stanford's claim of title and, more importantly, the rights and interests of the United States, to be frustrated by so dubious an assignment and so stale a claim cannot be correct.

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted,

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APPENDIX

APPENDIX A

35 U.S.C. Chapter 18 § 200 *et seq.* provides:

CHAPTER 18—PATENT RIGHTS IN INVENTIONS MADE WITH FEDERAL ASSISTANCE

Sec.
200. Policy and objective.
201. Definitions.
202. Disposition of rights.
203. March-in rights.
204. Preference for United States industry.
205. Confidentiality.
206. Uniform clauses and regulations.
207. Domestic and foreign protection of federally owned inventions.
208. Regulations governing Federal licensing.
209. Licensing federally owned inventions.
210. Precedence of chapter.
211. Relationship to antitrust laws.
212. Disposition of rights in educational awards.

§ 200. Policy and objective

It is the policy and objective of the Congress to use the patent system to promote the utilization of inventions arising from federally supported research or development; to encourage maximum participation of small business firms in federally supported research and development efforts; to promote collaboration between commercial concerns and nonprofit organizations, including universities; to ensure that inventions made by nonprofit

organizations and small business firms are used in a manner to promote free competition and enterprise without unduly encumbering future research and discovery; to promote the commercialization and public availability of inventions made in the United States by United States industry and labor; to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions; and to minimize the costs of administering policies in this area.

§ 201. Definitions

As used in this chapter—

(a) The term "Federal agency" means any executive agency as defined in section 105 of title 5, and the military departments as defined by section 102 of title 5.

(b) The term "funding agreement" means any contract, grant, or cooperative agreement entered into between any Federal agency, other than the Tennessee Valley Authority, and any contractor for the performance of experimental, developmental, or research work funded in whole or in part by the Federal Government. Such term includes any assignment, substitution of parties, or subcontract of any type entered into for the performance of experimental, developmental, or research work under a funding agreement as herein defined.

(c) The term "contractor" means any person, small business firm, or nonprofit organization that is a party to a funding agreement.

(d) The term "invention" means any invention or discovery which is or may be patentable or otherwise

protectable under this title or any novel variety of plant which is or may be protectable under the Plant Variety Protection Act (7 U.S.C. 2321 et seq.).

(e) The term "subject invention" means any invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement: *Provided,* That in the case of a variety of plant, the date of determination (as defined in section 41(d)[1] of the Plant Variety Protection Act (7 U.S.C. 2401(d))) must also occur during the period of contract performance.

(f) The term "practical application" means to manufacture in the case of a composition or product, to practice in the case of a process or method, or to operate in the case of a machine or system; and, in each case, under such conditions as to establish that the invention is being utilized and that its benefits are to the extent permitted by law or Government regulations available to the public on reasonable terms.

(g) The term "made" when used in relation to any invention means the conception or first actual reduction to practice of such invention.

(h) The term "small business firm" means a small business concern as defined at section 2 of Public Law 85–536 (15 U.S.C. 632) and implementing regulations of the Administrator of the Small Business Administration.

(i) The term "nonprofit organization" means universities and other institutions of higher education or an organization of the type described in section 501(c)(3) of the Internal Revenue Code of 1986 (26 U.S.C. 501(c)) and exempt from taxation

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[1] See References in Text note below. [Omitted]

under section 501(a) of the Internal Revenue Code (26 U.S.C. 501(a)) or any nonprofit scientific or educational organization qualified under a State nonprofit organization statute.

§ 202. Disposition of rights

(a) Each nonprofit organization or small business firm may, within a reasonable time after disclosure as required by paragraph (c)(1) of this section, elect to retain title to any subject invention: *Provided, however,* That a funding agreement may provide otherwise (i) when the contractor is not located in the United States or does not have a place of business located in the United States or is subject to the control of a foreign government, (ii) in exceptional circumstances when it is determined by the agency that restriction or elimination of the right to retain title to any subject invention will better promote the policy and objectives of this chapter[,] (iii) when it is determined by a Government authority which is authorized by statute or Executive order to conduct foreign intelligence or counter-intelligence activities that the restriction or elimination of the right to retain title to any subject invention is necessary to protect the security of such activities or, (iv) when the funding agreement includes the operation of a Government-owned, contractor-operated facility of the Department of Energy primarily dedicated to that Department's naval nuclear propulsion or weapons related programs and all funding agreement limitations under this subparagraph on the contractor's right to elect title to a subject invention are limited to inventions occurring under the above two programs of the Department of Energy. The rights of the nonprofit organization or small business

firm shall be subject to the provisions of paragraph (c) of this section and the other provisions of this chapter.

(b)(1) The rights of the Government under subsection (a) shall not be exercised by a Federal agency unless it first determines that at least one of the conditions identified in clauses (i) through (iv) of subsection (a) exists. Except in the case of subsection (a)(iii), the agency shall file with the Secretary of Commerce, within thirty days after the award of the applicable funding agreement, a copy of such determination. In the case of a determination under subsection (a)(ii), the statement shall include an analysis justifying the determination. In the case of determinations applicable to funding agreements with small business firms, copies shall also be sent to the Chief Counsel for Advocacy of the Small Business Administration. If the Secretary of Commerce believes that any individual determination or pattern of determinations is contrary to the policies and objectives of this chapter or otherwise not in conformance with this chapter, the Secretary shall so advise the head of the agency concerned and the Administrator of the Office of Federal Procurement Policy, and recommend corrective actions.

(2) Whenever the Administrator of the Office of Federal Procurement Policy has determined that one or more Federal agencies are utilizing the authority of clause (i) or (ii) of subsection (a) of this section in a manner that is contrary to the policies and objectives of this chapter, the Administrator is authorized to issue regulations describing classes of situations in which agencies may not exercise the authorities of those clauses.

(3) If the contractor believes that a determination is contrary to the policies and objectives of this chapter or constitutes an abuse of discretion by the agency, the determination shall be subject to the[1] section 203(b).

(c) Each funding agreement with a small business firm or nonprofit organization shall contain appropriate provisions to effectuate the following:

(1) That the contractor disclose each subject invention to the Federal agency within a reasonable time after it becomes known to contractor personnel responsible for the administration of patent matters, and that the Federal Government may receive title to any subject invention not disclosed to it within such time.

(2) That the contractor make a written election within two years after disclosure to the Federal agency (or such additional time as may be approved by the Federal agency) whether the contractor will retain title to a subject invention: *Provided*, That in any case where publication, on sale, or public use, has initiated the one year statutory period in which valid patent protection can still be obtained in the United States, the period for election may be shortened by the Federal agency to a date that is not more than sixty days prior to the end of the statutory period: *And provided further*, That the Federal Government may receive title to any subject invention in which the contractor does not elect to

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[1] So in original. The word "the" probably should not appear.

retain rights or fails to elect rights within such times.

(3) That a contractor electing rights in a subject invention agrees to file a patent application prior to any statutory bar date that may occur under this title due to publication, on sale, or public use, and shall thereafter file corresponding patent applications in other countries in which it wishes to retain title within reasonable times, and that the Federal Government may receive title to any subject inventions in the United States or other countries in which the contractor has not filed patent applications on the subject invention within such times.

(4) With respect to any invention in which the contractor elects rights, the Federal agency shall have a nonexclusive, nontransferrable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world: *Provided*, That the funding agreement may provide for such additional rights, including the right to assign or have assigned foreign patent rights in the subject invention, as are determined by the agency as necessary for meeting the obligations of the United States under any treaty, international agreement, arrangement of cooperation, memorandum of understanding, or similar arrangement, including military agreement relating to weapons development and production.

(5) The right of the Federal agency to require periodic reporting on the utilization or efforts at obtaining utilization that are being made by the contractor or his licensees or assignees: *Provided*,

That any such information as well as any information on utilization or efforts at obtaining utilization obtained as part of a proceeding under section 203 of this chapter shall be treated by the Federal agency as commercial and financial information obtained from a person and privileged and confidential and not subject to disclosure under section 552 of title 5.

(6) An obligation on the part of the contractor, in the event a United States patent application is filed by or on its behalf or by any assignee of the contractor, to include within the specification of such application and any patent issuing thereon, a statement specifying that the invention was made with Government support and that the Government has certain rights in the invention.

(7) In the case of a nonprofit organization, (A) a prohibition upon the assignment of rights to a subject invention in the United States without the approval of the Federal agency, except where such assignment is made to an organization which has as one of its primary functions the management of inventions (provided that such assignee shall be subject to the same provisions as the contractor); (B) a requirement that the contractor share royalties with the inventor; (C) except with respect to a funding agreement for the operation of a Government-owned-contractor-operated facility, a requirement that the balance of any royalties or income earned by the contractor with respect to subject inventions, after payment of expenses (including payments to inventors) incidental to the administration of subject inventions, be utilized for the support of scientific research or education; (D) a requirement that,

except where it proves infeasible after a reasonable inquiry, in the licensing of subject inventions shall be given to small business firms; and (E) with respect to a funding agreement for the operation of a Government-owned-contractor-operated facility, requirements (i) that after payment of patenting costs, licensing costs, payments to inventors, and other expenses incidental to the administration of subject inventions, 100 percent of the balance of any royalties or income earned and retained by the contractor during any fiscal year up to an amount equal to 5 percent of the annual budget of the facility, shall be used by the contractor for scientific research, development, and education consistent with the research and development mission and objectives of the facility, including activities that increase the licensing potential of other inventions of the facility; provided that if said balance exceeds 5 percent of the annual budget of the facility, that 75 percent of such excess shall be paid to the Treasury of the United States and the remaining 25 percent shall be used for the same purposes as described above in this clause (D); and (ii) that, to the extent it provides the most effective technology transfer, the licensing of subject inventions shall be administered by contractor employees on location at the facility.

(8) The requirements of sections 203 and 204 of this chapter.

(d) If a contractor does not elect to retain title to a subject invention in cases subject to this section, the Federal agency may consider and after consultation with the contractor grant requests for retention of

rights by the inventor subject to the provisions of this Act and regulations promulgated hereunder.

(e) In any case when a Federal employee is a coinventor of any invention made with a nonprofit organization, a small business firm, or a non-Federal inventor, the Federal agency employing such coinventor may, for the purpose of consolidating rights in the invention and if it finds that it would expedite the development of the invention—

(1) license or assign whatever rights it may acquire in the subject invention to the nonprofit organization, small business firm, or non-Federal inventor in accordance with the provisions of this chapter; or

(2) acquire any rights in the subject invention from the nonprofit organization, small business firm, or non-Federal inventor, but only to the extent the party from whom the rights are acquired voluntarily enters into the transaction and no other transaction under this chapter is conditioned on such acquisition.

(f)(1) No funding agreement with a small business firm or nonprofit organization shall contain a provision allowing a Federal agency to require the licensing to third parties of inventions owned by the contractor that are not subject inventions unless such provision has been approved by the head of the agency and a written justification has been signed by the head of the agency. Any such provision shall clearly state whether the licensing may be required in connection with the practice of a subject invention, a specifically identified work object, or both. The head of the agency may not delegate the authority to approve provisions or sign justifications required by this paragraph.

(2) A Federal agency shall not require the licensing of third parties under any such provision unless the head of the agency determines that the use of the invention by others is necessary for the practice of a subject invention or for the use of a work object of the funding agreement and that such action is necessary to achieve the practical application of the subject invention or work object. Any such determination shall be on the record after an opportunity for an agency hearing. Any action commenced for judicial review of such determination shall be brought within sixty days after notification of such determination.

§ 203. March-in rights

(a) With respect to any subject invention in which a small business firm or nonprofit organization has acquired title under this chapter, the Federal agency under whose funding agreement the subject invention was made shall have the right, in accordance with such procedures as are provided in regulations promulgated hereunder to require the contractor, an assignee or exclusive licensee of a subject invention to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable under the circumstances, and if the contractor, assignee, or exclusive licensee refuses such request, to grant such a license itself, if the Federal agency determines that such—

(1) action is necessary because the contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject invention in such field of use;

(2) action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees;

(3) action is necessary to meet requirements for public use specified by Federal regulations and such requirements are not reasonably satisfied by the contractor, assignee, or licensees; or

(4) action is necessary because the agreement required by section 204 has not been obtained or waived or because a licensee of the exclusive right to use or sell any subject invention in the United States is in breach of its agreement obtained pursuant to section 204.

(b) A determination pursuant to this section or section 202(b)(4)[1] shall not be subject to the Contract Disputes Act (41 U.S.C. § 601 et seq.). An administrative appeals procedure shall be established by regulations promulgated in accordance with section 206. Additionally, any contractor, inventor, assignee, or exclusive licensee adversely affected by a determination under this section may, at any time within sixty days after the determination is issued, file a petition in the United States Court of Federal Claims, which shall have jurisdiction to determine the appeal on the record and to affirm, reverse, remand or modify, as appropriate, the determination of the Federal agency. In cases described in paragraphs (1) and (3) of subsection (a), the agency's determination shall be held in abeyance pending the exhaustion of appeals or petitions filed under the preceding sentence.

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[1] See References in Text note below. [Omitted]

§ 204. Preference for United States industry

Notwithstanding any other provision of this chapter, no small business firm or nonprofit organization which receives title to any subject invention and no assignee of any such small business firm or nonprofit organization shall grant to any person the exclusive right to use or sell any subject invention in the United States unless such person agrees that any products embodying the subject invention or produced through the use of the subject invention will be manufactured substantially in the United States. However, in individual cases, the requirement for such an agreement may be waived by the Federal agency under whose funding agreement the invention was made upon a showing by the small business firm, nonprofit organization, or assignee that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible.

§ 205. Confidentiality

Federal agencies are authorized to withhold from disclosure to the public information disclosing any invention in which the Federal Government owns or may own a right, title, or interest (including a nonexclusive license) for a reasonable time in order for a patent application to be filed. Furthermore, Federal agencies shall not be required to release copies of any document which is part of an application for patent filed with the United States Patent and Trademark Office or with any foreign patent office.

§ 206. Uniform clauses and regulations

The Secretary of Commerce may issue regulations which may be made applicable to Federal agencies implementing the provisions of sections 202 through 204 of this chapter and shall establish standard funding agreement provisions required under this chapter. The regulations and the standard funding agreement shall be subject to public comment before their issuance.

§ 207. Domestic and foreign protection of federally owned inventions

(a) Each Federal agency is authorized to—

(1) apply for, obtain, and maintain patents or other forms of protection in the United States and in foreign countries on inventions in which the Federal Government owns a right, title, or interest;

(2) grant nonexclusive, exclusive, or partially exclusive licenses under federally owned inventions, royalty-free or for royalties or other consideration, and on such terms and conditions, including the grant to the licensee of the right of enforcement pursuant to the provisions of chapter 29 of this title as determined appropriate in the public interest;

(3) undertake all other suitable and necessary steps to protect and administer rights to federally owned inventions on behalf of the Federal Government either directly or through contract, including acquiring rights for and administering royalties to the Federal Government in any invention, but only to the extent the party from whom the rights are acquired voluntarily enters

into the transaction, to facilitate the licensing of a federally owned invention; and

(4) transfer custody and administration, in whole or in part, to another Federal agency, of the right, title, or interest in any federally owned invention.

(b) For the purpose of assuring the effective management of Government-owned inventions, the Secretary of Commerce is authorized to—

(1) assist Federal agency efforts to promote the licensing and utilization of Governmentowned inventions;

(2) assist Federal agencies in seeking protection and maintaining inventions in foreign countries, including the payment of fees and costs connected therewith; and

(3) consult with and advise Federal agencies as to areas of science and technology research and development with potential for commercial utilization.

§ 208. Regulations governing Federal licensing

The Secretary of Commerce is authorized to promulgate regulations specifying the terms and conditions upon which any federally owned invention, other than inventions owned by the Tennessee Valley Authority, may be licensed on a nonexclusive, partially exclusive, or exclusive basis.

§ 209. Licensing federally owned inventions

(a) AUTHORITY.—A Federal agency may grant an exclusive or partially exclusive license on a federally owned invention under section 207(a)(2) only if—

(1) granting the license is a reasonable and necessary incentive to—

(A) call forth the investment capital and expenditures needed to bring the invention to practical application; or

(B) otherwise promote the invention's utilization by the public;

(2) the Federal agency finds that the public will be served by the granting of the license, as indicated by the applicant's intentions, plans, and ability to bring the invention to practical application or otherwise promote the invention's utilization by the public, and that the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application, as proposed by the applicant, or otherwise to promote the invention's utilization by the public;

(3) the applicant makes a commitment to achieve practical application of the invention within a reasonable time, which time may be extended by the agency upon the applicant's request and the applicant's demonstration that the refusal of such extension would be unreasonable;

(4) granting the license will not tend to substantially lessen competition or create or maintain a violation of the Federal antitrust laws; and

(5) in the case of an invention covered by a foreign patent application or patent, the interests of the Federal Government or United States industry in foreign commerce will be enhanced.

(b) MANUFACTURE IN UNITED STATES.—A Federal agency shall normally grant a license under section 207(a)(2) to use or sell any federally owned invention in the United States only to a licensee who agrees

that any products embodying the invention or produced through the use of the invention will be manufactured substantially in the United States.

(c) SMALL BUSINESS.—First preference for the granting of any exclusive or partially exclusive licenses under section 207(a)(2) shall be given to small business firms having equal or greater likelihood as other applicants to bring the invention to practical application within a reasonable time.

(d) TERMS AND CONDITIONS.—Any licenses granted under section 207(a)(2) shall contain such terms and conditions as the granting agency considers appropriate, and shall include provisions—

(1) retaining a nontransferrable, irrevocable, paid-up license for any Federal agency to practice the invention or have the invention practiced throughout the world by or on behalf of the Government of the United States;

(2) requiring periodic reporting on utilization of the invention, and utilization efforts, by the licensee, but only to the extent necessary to enable the Federal agency to determine whether the terms of the license are being complied with, except that any such report shall be treated by the Federal agency as commercial and financial information obtained from a person and privileged and confidential and not subject to disclosure under section 552 of title 5; and

(3) empowering the Federal agency to terminate the license in whole or in part if the agency determines that—

(A) the licensee is not executing its commitment to achieve practical application of the invention, including commitments contained in any plan submitted in support of

its request for a license, and the licensee cannot otherwise demonstrate to the satisfaction of the Federal agency that it has taken, or can be expected to take within a reasonable time, effective steps to achieve practical application of the invention;

(B) the licensee is in breach of an agreement described in subsection (b);

(C) termination is necessary to meet requirements for public use specified by Federal regulations issued after the date of the license, and such requirements are not reasonably satisfied by the licensee; or

(D) the licensee has been found by a court of competent jurisdiction to have violated the Federal antitrust laws in connection with its performance under the license agreement.

(e) PUBLIC NOTICE.—No exclusive or partially exclusive license may be granted under section 207(a)(2) unless public notice of the intention to grant an exclusive or partially exclusive license on a federally owned invention has been provided in an appropriate manner at least 15 days before the license is granted, and the Federal agency has considered all comments received before the end of the comment period in response to that public notice. This subsection shall not apply to the licensing of inventions made under a cooperative research and development agreement entered into under section 12 of the Stevenson- Wydler Technology Innovation Act of 1980 (15 U.S.C. 3710a).

(f) PLAN.—No Federal agency shall grant any license under a patent or patent application on a federally owned invention unless the person requesting the license has supplied the agency with a

plan for development or marketing of the invention, except that any such plan shall be treated by the Federal agency as commercial and financial information obtained from a person and privileged and confidential and not subject to disclosure under section 552 of title 5.

§ 210. Precedence of chapter

(a) This chapter shall take precedence over any other Act which would require a disposition of rights in subject inventions of small business firms or nonprofit organizations contractors in a manner that is inconsistent with this chapter, including but not necessarily limited to the following:

(1) section 10(a) of the Act of June 29, 1935, as added by title I of the Act of August 14, 1946 (7 U.S.C. 427i(a); 60 Stat. 1085);

(2) section 205(a) of the Act of August 14, 1946 (7 U.S.C. 1624(a); 60 Stat. 1090);

(3) section 501(c) of the Federal Mine Safety and Health Act of 1977 (30 U.S.C. 951(c); 83 Stat. 742);

(4) section 30168(e) of title 49;

(5) section 12 of the National Science Foundation Act of 1950 (42 U.S.C. 1871(a);[1] 82 Stat. 360);

(6) section 152 of the Atomic Energy Act of 1954 (42 U.S.C. 2182; 68 Stat. 943);

(7) section 305 of the National Aeronautics and Space Act of 1958 (42 U.S.C. 2457);

(8) section 6 of the Coal Research and Development Act of 1960 (30 U.S.C. 666; 74 Stat. 337);

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[1] See References in Text note below. [Omitted]

(9) section 4 of the Helium Act Amendments of 1960 (50 U.S.C. 167b; 74 Stat. 920);

(10) section 32 of the Arms Control and Disarmament Act of 1961 (22 U.S.C. 2572; 75 Stat. 634);

(11) section 9 of the Federal Nonnuclear Energy Research and Development Act of 1974 (42 U.S.C. 5908; 88 Stat. 1878);

(12) section 5(d) of the Consumer Product Safety Act (15 U.S.C. 2054(d); 86 Stat. 1211);

(13) section 3 of the Act of April 5, 1944 (30 U.S.C. 323; 58 Stat. 191);[1]

(14) section 8001(c)(3) of the Solid Waste Disposal Act (42 U.S.C. 6981(c); 90 Stat. 2829);

(15) section 219 of the Foreign Assistance Act of 1961 (22 U.S.C. 2179; 83 Stat. 806);

(16) section 427(b) of the Federal Mine Health and Safety Act of 1977 (30 U.S.C. 937(b); 86 Stat. 155);

(17) section 306(d) of the Surface Mining and Reclamation Act of 1977 (30 U.S.C. 1226(d); 91 Stat. 455);[1]

(18) section 21(d) of the Federal Fire Prevention and Control Act of 1974 (15 U.S.C. 2218(d); 88 Stat. 1548);

(19) section 6(b) of the Solar Photovoltaic Energy Research Development and Demonstration Act of 1978 (42 U.S.C. 5585(b); 92 Stat. 2516);

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[1] See References in Text note below. [Omitted]

(20) section 12 of the Native Latex Commercialization and Economic Development Act of 1978 (7 U.S.C. 178j; 92 Stat. 2533); and

(21) section 408 of the Water Resources and Development Act of 1978 (42 U.S.C. 7879; 92 Stat. 1360).

The Act creating this chapter shall be construed to take precedence over any future Act unless that Act specifically cites this Act and provides that it shall take precedence over this Act.

(b) Nothing in this chapter is intended to alter the effect of the laws cited in paragraph (a) of this section or any other laws with respect to the disposition of rights in inventions made in the performance of funding agreements with persons other than nonprofit organizations or small business firms.

(c) Nothing in this chapter is intended to limit the authority of agencies to agree to the disposition of rights in inventions made in the performance of work under funding agreements with persons other than nonprofit organizations or small business firms in accordance with the Statement of Government Patent Policy issued on February 18, 1983, agency regulations, or other applicable regulations or to otherwise limit the authority of agencies to allow such persons to retain ownership of inventions except that all funding agreements, including those with other than small business firms and nonprofit organizations, shall include the requirements established in section 202(c)(4) and section 203 of this title. Any disposition of rights in inventions made in accordance with the Statement or implementing regulations, including any disposition occurring before enactment of this section, are hereby authorized.

(d) Nothing in this chapter shall be construed to require the disclosure of intelligence sources or methods or to otherwise affect the authority granted to the Director of Central Intelligence by statute or Executive order for the protection of intelligence sources or methods.

(e) The provisions of the Stevenson-Wydler Technology Innovation Act of 1980 shall take precedence over the provisions of this chapter to the extent that they permit or require a disposition of rights in subject inventions which is inconsistent with this chapter.

§ 211. Relationship to antitrust laws

Nothing in this chapter shall be deemed to convey to any person immunity from civil or criminal liability, or to create any defenses to actions, under any antitrust law.

§ 212. Disposition of rights in educational awards

No scholarship, fellowship, training grant, or other funding agreement made by a Federal agency primarily to an awardee for educational purposes will contain any provision giving the Federal agency any rights to inventions made by the awardee.

RESPONDENT'S BRIEF

No. 09-1159

FILED
2011
CLERK

IN THE

Supreme Court of the United States

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR RESPONDENTS

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QUESTION PRESENTED

The Bayh-Dole Act limits the government's intellectual property rights by providing that federal contractors may "elect to retain title" to any "invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement." 35 U.S.C. §§ 201(e), 202(a).

In this case, a researcher obtained access to a private company's resources and expertise in exchange for a written assignment of his interest in any resulting invention. An invention was conceived while the researcher was at the company using its proprietary materials and know-how, thus triggering the assignment provision. Clinical trials involving the already-conceived invention later took place at Stanford University and, according to Stanford, proceeded under a funding agreement between Stanford and the National Institutes of Health.

The question presented is:

Whether the Bayh-Dole Act's provision allowing a federal contractor to "elect to retain title" to an "invention of the contractor" allows the contractor retroactively to take intellectual property rights that have been validly assigned to a third party that neither accepted nor benefitted from federal funds.

CORPORATE DISCLOSURE STATEMENT

Pursuant to the Court's Rule 29.6, Respondents state as follows:

1. Roche Molecular Systems, Inc., a Delaware corporation, is a wholly-owned subsidiary of Roche Holdings, Inc., a Delaware corporation, which is a subsidiary of Roche Finance Ltd, which is a subsidiary of Roche Holding Ltd. More than 10% of Roche Holding Ltd's voting shares are held by Novartis International Ltd (Switzerland) as direct holder, with its parent Novartis AG (Switzerland) as economic beneficiary.

2. Roche Diagnostics Corporation, an Indiana corporation, is a wholly-owned subsidiary of Roche Holdings, Inc.

3. Roche Diagnostics Operations, Inc., a Delaware corporation, is a wholly-owned subsidiary of Roche Holdings, Inc.

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IN THE

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No. 09-1159

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

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v.

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Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR RESPONDENTS

INTRODUCTION

The collaboration at the heart of this case rested on the principle that inventions and patents are owned by their inventor, subject to transfer by written assignment or other recognized means for conveying personal property. 35 U.S.C. §§ 101, 261. In exchange for access to Cetus Corporation's scientific expertise and proprietary materials, Dr. Mark Holodniy assigned any resulting inventions to Cetus. The inventions claimed in the patents-in-suit were conceived at Cetus during this collaboration. Under federal patent and state contract

law, title vested in Holodniy and was assigned to Cetus, giving both sides the benefit of their bargain.

Stanford claims, however, that established principles of ownership and assignment were swept aside by the Bayh-Dole Act, which it believes to be a "vesting" statute "automatically" granting "perfect" title to federal contractors if any amount of federal funding is involved at any point in the process—even if the invention would otherwise have been owned by a third party, such as an individual inventor or his assignee. The Act says nothing of the sort. Rather, it limits the *government's* rights in inventions it helped to fund. The Act creates a system—implemented through bilateral funding agreements between the government and its contractors—under which a contractor may "retain title" to any "invention of the contractor" that is "conceived or first actually reduced to practice in the performance of work under a funding agreement." 35 U.S.C. §§ 201(e), 202(a). As the words "invention of the contractor" confirm—and the remainder of the Act reinforces—the Act applies only to inventions that the contractor otherwise owns under established principles of law. It does not purport to alter those principles, much less do so *sub silentio*.

Stanford's contrary arguments consist mostly of isolated passages of legislative history and misdirected policy arguments. Correctly viewed, none supports Stanford, nor would they justify rewriting the Act if they did. They certainly do not justify eliminating, retroactively and without notice or procedural protection, the intellectual property rights a third party receives in exchange for valuable contributions to an invention. The Court should affirm.

STATEMENT

A. Cetus's Groundbreaking Discovery Of PCR And Its Application To Measuring HIV

In the mid-1980s, Dr. Kary Mullis, a researcher at a small California startup called Cetus Corporation, discovered the polymerase chain reaction (PCR), a technique that allows scientists to make billions of copies of DNA sequences from a small number of starting molecules. Pet. App. 32a. PCR earned Dr. Mullis the Nobel Prize in Chemistry and is now a foundational tool of genetic and biological innovation. *Id.*

In 1985, Cetus began to examine the use of PCR to detect and quantify blood-borne levels of human immunodeficiency virus (HIV), which causes AIDS. Pet. App. 32a. In 1988, Cetus collaborated with Stanford University scientists Thomas Merigan and David Schwartz in the clinical trial of an AIDS drug, during which "the Cetus team used PCR to quantitate the HIV levels of the participating patients." *Id.* 32a-33a.

B. Stanford Sends Holodniy To Cetus To Develop A PCR Assay For HIV

This case turns on work that Dr. Mark Holodniy performed at Cetus in 1989. Holodniy had joined Stanford in July 1988. After a "few months in clinical rotations," Holodniy "began focusing on possible research projects." Pet. App. 94a. He joined Merigan's lab, and they determined that Holodniy should "direct [his] research to developing a better quantitative PCR-based assay for HIV." *Id.*

Holodniy had no prior experience with quantitation assays or PCR. J.A. 49-52; Pet. App. 36a. Merigan and Schwartz likewise lacked substantial PCR experience, and—as Holodniy later wrote—the development of a

quantitation assay for HIV "proved to be difficult." C.A.J.A. 4836. Merigan and Holodniy eventually "decided that it would be helpful to work with Cetus scientists to develop an HIV assay." Pet. App. 95a.

Merigan, who sat on Cetus's scientific advisory board, arranged for Holodniy to work at Cetus. Pet. App. 31a; J.A. 29, 87-88. Holodniy "began commuting daily to Cetus," "was assigned a lab bench ... , and had access to Cetus personnel, materials, and equipment." Pet. App. 35a. Holodniy spent approximately nine months at Cetus, "receiving technical information from Cetus scientists and proprietary physical materials." *Id.* 36a. Holodniy went to Cetus "for access to certain reagents, certain equipment, [and] certain computer programs, ... to generate primers and to consult with members of Cetus on scientific issues." J.A. 90.

As consideration for this access, Holodniy signed a "Visitor Confidentiality Agreement" (VCA), which assigned to Cetus Holodniy's "right, title, and interest" in any invention made "as a consequence of [his] access" to Cetus facilities. Pet. App. 35a-36a (quoting VCA); J.A. 93. As both courts below ruled, the inventions at issue arose "as a consequence of" Holodniy's access to Cetus, triggering the VCA's assignment provision. Pet. App. 15a, 64a-65a. Although Stanford had previously required Holodniy to execute a "Copyright and Patent Agreement" (CPA), that document stated only that Holodniy "agree[d] to assign" his "inventions as required by Contracts or Grants" (*id.* 118a-119a)—language that merely obligated Holodniy to execute a *later* assignment of any covered invention (*id.* 13a). The VCA, by contrast, immediately assigned to Cetus any inventions within its scope upon their conception. *Id.* 14a. Because Holodniy went to Cetus as Stanford's

agent, Stanford was chargeable with notice of Holodniy's execution of the VCA. *Id.* 16a-17a, 64a.

C. The Claimed Inventions Are Conceived At Cetus In 1989 Without Use Of Bayh-Dole Funding

The Cetus research "focused on quantitation of HIV-1 RNA in serum or plasma, using PCR techniques, in the hope that RNA levels would also correlate with the stage of HIV-1 disease and response to treatment." C.A.J.A. 4837. "By early Fall of 1989," *i.e.*, while Holodniy was still at Cetus, "a working assay for the quantitation of HIV RNA" had been constructed. J.A. 29. As the district court found, that assay consisted of five steps:

> (1) extracting HIV RNA;
>
> (2) producing a DNA molecule through reverse transcription;
>
> (3) using PCR to amplify the DNA using primers developed by Cetus;
>
> (4) detecting the amplified DNA; and
>
> (5) generating a standard curve used to calculate the amount of virus in a patient's blood using a cRNA standard ("quantitation").

Pet. App. 36a. The district court ruled that the invention claimed in the patents-in-suit—the use of the PCR-based assay to quantitate HIV in patient blood and thereby track therapy or disease progression—was fully conceived while Holodniy was at Cetus. *Id.* 56a.

Holodniy did not develop the assay by himself; he worked with several Cetus scientists and learned "the techniques related to the cellular DNA and RNA quan-

titation and then the serum HIV RNA quantitation" from them. J.A. 69-71. Prior to visiting Cetus, Holodniy had never built a quantitation assay, run a PCR product, amplified or quantified HIV RNA, or even "done any previous work in that field." J.A. 49, 55-57. Holodniy's work at Cetus thus made use of "technical information from Cetus scientists and proprietary physical materials from Cetus." Pet. App. 36a; *accord* J.A. 29-31, 58-63. Holodniy "sought the assistance of Cetus scientist Alice Wang to develop the quantitation portion of the assay." Pet. App. 36a. The "cRNA standard" used in step (5) was developed by Cetus employee Clayton Casipit (and named CC2, using Casipit's initials) and given to Holodniy in October 1989. *Id.* 36a-37a; J.A. 29. The primers used in the assay, known as SK38, SK39, and SK19-HRP, were developed by (and named after) Cetus employee Shirley Kwok. J.A. 74. Holodniy's lab notebook reflects the many contributions that Cetus scientists made to his work, including his critical reliance on these materials and the fact that he received them from Cetus. J.A. 80-81; Supp. J.A. 7, 9, 11.

Stanford now suggests—for the first time—that Holodniy's work before or during his time at Cetus was funded by Bayh-Dole money, but no evidence supports that claim. In fact, Stanford repeatedly asserted below that the Bayh-Dole Act was implicated through "federally funded clinical research at Stanford *beginning in July 1990*" (Stanford C.A. Reply 43), "after [Holodniy] was no longer a visitor at Cetus" (*id.* 12).[1] Stanford

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[1] *See also* Stanford C.A. Br. 2 (inventions "arose out of research conducted in the early 1990s"); Stanford C.A. Reply 7 ("clinical research giving rise to the claimed inventions" occurred "under at least two government grants" and "did not begin until

failed to produce the two NIH grant agreements on which it relies (J.A. 103), and it is undisputed that Holodniy's salary at Cetus was paid not by either grant, but by a National Research Service Award of the kind expressly exempted from the Bayh-Dole Act. J.A. 98 ¶13, 109-117; 35 U.S.C. § 212.

D. Holodniy And Cetus Scientists Publish The Assay

In December 1989, pursuant to his obligations under the VCA (Pet. App. 122a-123a), Holodniy sought Cetus's permission to publish the HIV assay in two conference abstracts (*id.* 37a). Cetus granted permission, but only after Holodniy added Cetus scientists as co-authors. *Id.*; *accord* J.A. 127-131, 132. Both abstracts not only described the steps of the quantitation assay, but noted that that "[q]uantitation of HIV-1 viral RNA in serum by PCR may be a useful marker for disease progression or monitoring antiviral therapy." J.A. 32, 131; C.A.J.A. 769-770. Neither abstract suggested that the work was funded by any federal grant.

Again pursuant to his VCA obligations, Holodniy submitted an invention disclosure to Cetus in January 1990, attaching one of the abstracts. Supp. J.A. 14. Further contradicting Stanford's recent suggestion that the claimed invention was supported by work at Stanford in 1988, Holodniy made plain on this form that he began working on the invention in September 1989.

July 1990, over seven months after Dr. Holodniy stopped visiting Cetus"); *id.* 58 (inventions made during clinical work "that began approximately nine months after Dr. Holodniy stopped visiting Cetus").

Id. 15. This disclosure also referenced no grant support.

In July 1990, Holodniy and other Stanford and Cetus co-authors submitted an article to the *Journal of Infectious Diseases* entitled "Detection and Quantification of Human Immunodeficiency Virus RNA in Patient Serum by Use of the Polymerase Chain Reaction" (the "JID article"). J.A. 135. The article observed a correlation between "[s]erum HIV RNA detected by PCR" and "the presence of HIV-related symptoms or disease"; it also stated that HIV RNA quantitation through PCR "may be useful as a marker for disease progression or in monitoring antiviral therapy." J.A. 136. The article concluded that "[s]erum PCR may provide an additional marker of disease progression and drug efficacy that could improve our ability to monitor the course of HIV infection. Further studies will be necessary to validate this approach." J.A. 148-149. Katzenstein, one of the Stanford co-authors, confirmed that the JID article was the "fulfillment" of the idea of using PCR to measure HIV RNA in order to monitor therapy and/or disease progression. J.A. 86. Holodniy likewise wrote that his work with Cetus "culminated" in this publication "on the correlation between HIV-1 load and stage of HIV-1 disease." C.A.J.A. 4837.

E. Stanford Conducts Clinical Trials In 1990 And Applies For Patents

Holodniy returned to Stanford in mid-October 1989. C.A.J.A. 4837. In July 1990, he and others began clinical trials using the PCR assay developed at Cetus and disclosed in the JID article. The purpose of these experiments was to "confirm[] the workability of the ... invention." Dkt. 96, at 29. During that time, Holodniy

continued to use Cetus materials. *E.g.*, Supp. J.A. 11 ("primers received from Cetus" "picked up 7-11-90").[2]

On May 14, 1992, Stanford filed the first of several patent applications for the inventions at issue. Although the original application listed only Merigan and Michael Kozal as inventors, Stanford filed a notice of correction of inventorship in November 1992 to add Holodniy and Katzenstein. Pet. App. 40a. As support for adding Holodniy as a co-inventor, Stanford's patent counsel declared that Holodniy's inventive contribution "principally concerns quantitation of HIV RNA in plasma of AIDS patients" (J.A. 154)—that is, the assay developed at Cetus.

In 1995, Stanford obtained written assignments from Holodniy, Merigan, and Katzenstein purporting to convey their interests in the pending patent applications. J.A. 42.

The first patent-in-suit (No. 5,968,730) issued in 1999; the two others issued in 2003 (No. 6,503,705) and 2006 (No. 7,129,041). All three are entitled "Polymerase Chain Reaction Assays for Monitoring Antiviral Therapy and Making Therapeutic Decisions in the Treatment of Acquired Immunodeficiency Syndrome." Supp. J.A. 17, 39, 64. As Stanford conceded and the patents' titles indicate, the asserted claims "include ... PCR assay steps like those disclosed in the JID arti-

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[2] Holodniy's work at Stanford in 1990 could not have been more than confirmation. The assay was tested on HIV patients at Cetus to measure HIV levels, as reported in the JID article. J.A. 135-136. The article also reported the assay's utility for assisting in monitoring disease. J.A. 85-86, 136, 148-149. The district court accordingly ruled that the article rendered the patents obvious. 563 F. Supp. 2d 1016, 1028 n.13 (N.D. Cal. 2008).

cle." Stanford C.A. Reply 25. Claim 1 of the '730 patent is representative and recites (1) "collecting" a plasma sample from an HIV patient, (2) "amplifying" the HIV-encoding nucleic acid in the sample using PCR; and (3) "testing for" the presence of HIV nucleic acids in the PCR product. Supp. J.A. 37. The claim then contains an additional limitation that, after the assay is performed, "the absence of detectable HIV-encoding nucleic acid correlates positively with the conclusion that the antiretroviral agent is therapeutically effective." *Id.*[3] In other words, the patents claim the PCR-based HIV assay that the parties agree was developed at Cetus and disclosed in the JID article (*see supra* pp. 7-8), plus a step in which a doctor evaluates whether treatment was effective by determining whether HIV RNA is present and whether the amount has gone up or down.

F. Roche Commercializes The Assay

In 1991, Roche acquired all of Cetus's PCR assets, including its rights under the VCA. Roche conducted clinical trials of a test kit for quantitating HIV RNA using PCR, including a trial on which Stanford's named inventor Merigan was a principal investigator. C.A.J.A. 4811; Dkt. 109-2, at 11. Roche's test kits went on sale in June 1996; Stanford University Hospital was among the first customers. C.A.J.A. 4815. Roche's kits

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[3] *See also* Supp. J.A. 61 ('705 patent cl. 1) (adding additional steps of "comparing" the "HIV RNA copy numbers" over the course of treatment and "evaluating whether a statistically significant decline" exists), 86 ('041 patent cl. 1) (claiming a method of "correlating the presence or absence of detectable HIV-encoding nucleic acid in a plasma sample" with a standard, using the PCR assay).

are used in hospitals and AIDS clinics worldwide, facilitating treatment for millions of patients.

In 2000, Stanford asserted that Roche could not sell its kits without obtaining a license from Stanford and paying a royalty. Pet. App. 109a-110a. There is no evidence that Stanford has otherwise attempted to commercialize these patents or use them to benefit public health.

G. District Court Proceedings

In 2005, Stanford sued Roche, asserting that the test kits Roche had been selling for nine years infringed the patents-in-suit. Roche asserted several affirmative defenses, including ownership and lack of standing based on Holodniy's assignment in the VCA. Dkt. 15 ¶¶27, 30. Roche also counterclaimed that at least one Cetus employee was a required co-inventor on the patents (*id.* ¶¶38, 43)—a claim that remains unresolved.[4]

Stanford first mentioned the Bayh-Dole Act when the parties cross-moved for summary judgment on Roche's claim of co-ownership. In response, Roche noted that Stanford had proffered neither the relevant grant agreements nor any evidence that the claimed inventions fell within their scope. Stanford's corporate designee testified that he "understood" that the inventions "were all funded by at least two U.S. government grants" (Pet. App. 109a), but admitted that he

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[4] Stanford's assertion that Roche has "[a]t no point ... disputed inventorship to assert that a non-Stanford-employee was a co-inventor" (Pet. Br. 33) is baffling. Indeed, *Stanford* sought summary judgment on Roche's inventorship claim (Dkt. 295, at 1-6), a motion the district court deemed withdrawn when it held the patents invalid (Dkt. 314).

had "[n]ever seen those contracts" and could not find them (J.A. 103). Although Merigan asserted by declaration (15 years after the fact) that "Holodniy's *research in my laboratory* was performed under two grants from [NIH]" (J.A. 98 (emphasis added)), that assertion both lacked support and failed even to suggest that Holodniy's work on the relevant *inventions* was federally funded.[5]

The district court ruled that Roche's ownership-related claims and affirmative defenses were time-barred. Pet. App. 49a, 51a. Nonetheless, "because the effect of the Holodniy VCA [was] raised and extensively argued," the court addressed the issue. *Id.* 53a. After considering the evidence in detail, the court concluded that the "the specific method of using the assay to monitor HIV treatment was ... clear in the minds of Holodniy and the other Stanford scientists when the assay was completed at Cetus." *Id.* 56a. The court thus ruled that "the invention was conceived during Holodniy's consultancy at Cetus," no later than October 1989. *Id.* 58a. Accordingly, "[t]he VCA effectively assigned any rights that Holodniy had in the patented inventions to Cetus." *Id.* 59a.[6]

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[5] The invention disclosure form Merigan submitted to Stanford mentioned two NIH grants, but did not include Holodniy as a co-inventor. Dkt. 110-6. During his deposition, Merigan mentioned NIH grants to "renovate" Stanford's facilities "to make it safer for managing viruses," but did not suggest that they funded PCR research by anyone, much less Holodniy. Dkt. 95-1, at 3.

[6] Though Stanford insisted that the claimed inventions were conceived after Holodniy left Cetus, it refused to disclose the actual conception date reflected in its documentation. Pet. App. 58a n.7; Dkt. 110-6 (redacted invention disclosure form).

The district court then addressed Stanford's argument under the Bayh-Dole Act. The court recognized that the Act did not automatically vest title in Stanford and "does not alter the general rule that title to a patent vests in the inventor or the designated assignee." Pet. App. 60a. The court concluded, however, that "Holodniy's purported assignment to Cetus conflicted with the legal requirements of the Bayh-Dole Act" and that the "assignment provision in the VCA [was] therefore void" as to the patents-in-suit. *Id.* 62a.

The court made no finding and cited no evidence demonstrating that Holodniy's work on the claimed inventions fell "under a funding agreement." 35 U.S.C. § 201(e). Nor did it address the Act's limitation to "invention[s] of the contractor" (*id.*) or explain how that provision could encompass Holodniy's or Cetus's interest in the patents-in-suit.

The court separately ruled that, because Holodniy "was sent to Cetus by Merigan" and "signed the VCA in the course of Stanford's business," Stanford had notice of the VCA as a matter of law and (but for the Bayh-Dole Act) would have been bound by the assignment to Cetus. Pet. App. 64a. The court rejected Stanford's contention that the inventions fell outside the VCA's scope: they were "unambiguously" developed "as a consequence of" Holodniy's access to Cetus, because he "spent nine months working onsite at Cetus, using Cetus equipment and materials and obtaining advice from Cetus personnel, and ... developed the PCR assay with assistance from Cetus scientists while [he] was at Cetus." *Id.* 64a-65a (internal quotation marks omitted).

The district court accordingly granted Stanford's summary judgment motion in part and denied Roche's motion in its entirety.

The district court later held the asserted patent claims obvious because the JID article "discloses the same PCR HIV assay that is disclosed in the asserted patents." 563 F. Supp. 2d 1016, 1024 (N.D. Cal. 2008). The court ruled that the difference between the JID article and the asserted claims was "solely the correlation and evaluation steps in the patents." *Id.* at 1044. It found that those steps—many of which merely amounted to looking at the results of the assay and concluding that a given treatment was effective if HIV levels decreased—were known in the prior art and that their combination with the assay disclosed in the article would have been obvious. *Id.* at 1045-1049.

H. Court Of Appeals Proceedings

Stanford appealed the invalidity judgment, and Roche cross-appealed the grant of summary judgment on the ownership issues. The Federal Circuit, in rulings not challenged here, held that Roche's defense based on the VCA was not time-barred and that the inventions were covered by the VCA because they were developed "'as a consequence' of [Holodniy's] access to Cetus." Pet. App. 9a-12a, 15a. The court also ruled that, under settled California law, "Stanford had at least constructive or inquiry notice of the VCA." *Id.* 16a; *see also id.* 17a ("For this purpose, there is no difference between constructive and actual notice." (quoting California law)). Although the Federal Circuit noted that the VCA would apply "[e]ven if Holodniy conceived and reduced to practice after departing Cetus" (*id.* 15a), it did not disturb the district court's

conclusion that the invention was conceived when the PCR assay was completed at Cetus.

With respect to the Bayh-Dole Act, the Federal Circuit observed that, "when the Bayh-Dole Act's provisions are violated," the government may take action, but nothing in the statute, regulations, or case law suggests that title is "automatically forfeited." Pet. App. 18a-19a. The court left open the question whether Holodniy's contracts or the Bayh-Dole Act gave the government or Stanford "some other legal recourse to recover Holodniy's rights." *Id.* 20a n.1.[7]

SUMMARY OF ARGUMENT

Nothing in the Bayh-Dole Act purports to upset the ordinary patent-law processes by which inventions are owned and assigned. The Act limits its application to "subject inventions," defined as "inventions of the contractor"—*i.e.*, inventions the contractor *already* owns. The Act provides that the contractor may "retain"—*i.e.*, keep—those inventions, notwithstanding any claim the government might have to the results of research it sponsors. It says nothing about third-party assignees like Cetus that receive intellectual property rights through valid assignments for consideration and that neither accept nor benefit from federal funds themselves. Congress knew how to write provisions that "vest" title; the Bayh-Dole Act contains none.

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[7] The Federal Circuit made no finding that the claimed inventions, and particularly Holodniy's inventive contributions to them, were funded by NIH, although it did state (without citation) that "Stanford received government funding for *its HIV research*." Pet. App. 5a (emphasis added).

Beyond the plain language of its operative provisions, the Act is structured to regulate the relationship between the government and its contractors, not third-party rights. The Act is implemented through detailed provisions to be included in funding agreements—provisions that necessarily cannot bind non-contracting parties. The Act also contains scrupulous procedural protections designed to ensure that the government does not trench on the rights of contractors, yet it provides no protection at all for third parties—an understandable situation if the Act does not divest third parties of their rights, but a startling omission if it does. Under Stanford's position, it can "take" title to a collaborative invention merely by *asserting*, without proving, that some undisclosed amount of federal funds under some undisclosed funding agreement was used to perform some undisclosed work at a time that, while itself undisclosed, came *after* the invention at issue was conceived using private funds. Such a result would be unsupported and constitutionally suspect.

The untoward results of Stanford's reading vanish when the Act is correctly understood against the backdrop of established rules vesting title to inventions in inventors, subject to their assignments. The government itself presumes that federal employees own their inventions, subject to obligations to assign them in many (but not all) cases. Universities, including Stanford, have operated on that basis as well, requiring faculty to execute assignments of inventions, including federally-funded inventions—actions that would be superfluous if the Act were an automatic "vesting" provision.

Treating the Act as regulating "inventions of the contractor"—rather than as transferring third-party rights to contractors without notice or opportunity to

protest—fully accords with Congress's goal. The legislative history is replete with criticism of bureaucratic inefficiency and the desire to move inventions off *government* shelves. But Stanford identifies not one statement suggesting that Congress viewed *third-party* rights obtained through valid contractual assignments as problematic, much less that general assignment principles should be altered.

Stanford's policy arguments are also deeply misdirected. Hundreds of billions of dollars of private investment flow annually to innovative research in this country without need for a federal statute "vesting" ownership in anyone but the inventor, and the Bayh-Dole Act itself has operated for 30 years without any suggestion (before this case) that it "vested" title. If anything, it is *Stanford's* position that would harm innovation by upsetting contractual expectations and discouraging private firms from collaborating with the academy. Stanford's hypotheticals regarding secret assignments, self-dealing professors, and conflicting contractual obligations can all be resolved under well-established patent and contract rules, as they are when they (rarely) arise in cases concerning privately-funded innovation.

Stanford ends its brief with an appeal to equity, a curious gambit given the facts of this case. Cetus did everything it could do to permit an open collaboration while protecting its intellectual property rights, and then taught Holodniy everything he knew about PCR. Roche, Cetus's successor, uses the PCR assay in test kits that daily improve the treatment of patients afflicted with HIV. Stanford retains the right to practice or license the claimed inventions in competition with Roche. But Stanford does not want to compete; it wants to tax Roche's commercial products solely for its

own benefit. Such a result is far from equitable, and Stanford has shown no reason why the Court should create such an obstacle to private enterprise by rewriting a statute intended to limit *the government's* intellectual property rights.

ARGUMENT

I. THE BAYH-DOLE ACT DOES NOT "VEST TITLE"

A. The Text Addresses Only Inventions That The Contractor Otherwise Owns

1. "Invention of the contractor"

Construction of the Bayh-Dole Act "begin[s], as always, with the language of the statute." *Duncan* v. *Walker*, 533 U.S. 167, 172 (2001). By its terms, the Act applies only to "subject inventions," that is, "any invention *of the contractor* conceived or first actually reduced to practice in the performance of work under a funding agreement." 35 U.S.C. § 201(e) (emphasis added). This Court has ruled that "[t]he use of the word 'of' denotes ownership." *Poe* v. *Seaborn*, 282 U.S. 101, 109 (1930); *see also Ellis* v. *United States*, 206 U.S. 246, 259 (1907) (Holmes, J.) ("[T]he most natural meaning of 'of the United States' is 'belonging to the United States.'"); *Jacobs* v. *New York Foundling Hosp.*, 577 F.3d 93, 100 (2d Cir. 2009) ("[O]f is a word used to indicate belonging or a possessive relationship."); *cf. National Cable & Telecomm. Ass'n v. Gulf Power Co.*, 534 U.S. 327, 335 (2002) (distinguishing "by" from "of").

The Act sets forth no special rules for determining whether particular intellectual property is an "invention of the contractor." That is unsurprising, because Congress has elsewhere enacted, and courts have long interpreted, detailed rules governing ownership and assignment of inventions. The Patent Act provides

that "[w]hoever invents or discovers a new and useful [invention] may obtain a patent therefor" and that patents and patent applications are "assignable in law by an instrument in writing." 35 U.S.C. §§ 101, 261; *see also* 37 C.F.R. § 3.73 ("The inventor is presumed to be the owner of a patent application, and any patent that may issue therefrom, unless there is an assignment."). As this Court has recognized for over a century, title to an invention thus vests in its inventor, subject to transfer by written assignment. *See, e.g.*, *United States* v. *Dubilier Condenser Corp.*, 289 U.S. 178, 187 (1933); *Standard Parts Co.* v. *Peck*, 264 U.S. 52, 59 (1924); *Dalzell* v. *Dueber Watchcase Mfg. Co.*, 149 U.S. 315, 320 (1893); *Hapgood* v. *Hewitt*, 119 U.S. 226, 233 (1886). Expectant interests in inventions not yet in being may also be assigned in advance. *FilmTec Corp.* v. *Allied-Signal Inc.*, 939 F.2d 1568, 1572-1573 & n.8 (Fed. Cir. 1991).

The Bayh-Dole Act nowhere purports to upset these established principles, nor does it suggest that an invention's status as an "invention of the contractor" is to be determined by any other means. Accordingly, the Act governs only rights that otherwise *belong to the contractor*, who may be the inventor himself (*see* 35 U.S.C. § 201(c) (contractor may be a "person")) or his assignee or successor-in-interest. It does not affect rights "of" third parties that have not contracted with the federal government.

Stanford and its *amici* largely ignore the words "of the contractor," frequently asserting—incorrectly—that the Act applies to all "inventions arising from federally funded research." Pet. Br. 1, 11; *see also id.* 26 (quoting Section 201(e) but eliding the words "of the contractor"); U.S. Inv. Br. 4 (same). Stanford addresses "of the contractor" only once, arguing that

"[s]ince an institution can only *create* an invention through the actions of its employees, this language is naturally read to include all inventions *made by the contractor's employees* with the aid of federal funding." Pet. Br. 32 (emphasis added). Stanford's argument is doubly mistaken.

First, "of the contractor" is not "naturally read" to mean "created by the contractor" because inventions are "created" by people, not institutions. *See* 35 U.S.C. § 102; AIPLA Br. 18-19. Where Congress meant to refer to the *making* of an invention, Congress used that verb expressly. *See* 35 U.S.C. § 212 (Act excludes inventions "made by the awardee" of an educational grant). The more natural reading of "invention of the contractor" is "belonging to the contractor," not "made by one of the contractor's employees without regard to any assignment."

Second, contrary to Stanford's assumption, employers do not automatically own employee inventions. Rather, "an invention presumptively belongs to its creator, ... even though the invention was conceived and/or reduced to practice during the course of employment." *Teets* v. *Chromalloy Gas Turbine Corp.*, 83 F.3d 403, 407 (Fed. Cir. 1996) (citing *Hapgood*, 119 U.S. at 233-234). And as this Court has made clear, "title to [a patent] can pass only by assignment," even as between employer and employee. *Dubilier*, 289 U.S. at 187. Once again, nothing in the Bayh-Dole Act purports to upset these longstanding principles; rather, the Act is "naturally read" as *consistent* with them. *Samantar* v. *Yousuf*, 130 S. Ct. 2278, 2289 n.13 (2010) ("[W]hen a statute covers an issue previously governed by the common law, we interpret the statute with the presumption that Congress intended to retain the substance of the common law."); *Ruckelshaus* v. *Monsanto*

Co., 467 U.S. 986, 1018 (1984) ("[W]here two statutes are capable of co-existence, it is the duty of the courts, absent a clearly expressed congressional intention to the contrary, to regard each as effective." (internal quotation marks omitted)).

Stanford essentially reads the words "of the contractor" out of the Act, contrary to the canon that courts should "give effect, if possible, to every word Congress used." *Reiter* v. *Sonotone Corp.*, 442 U.S. 330, 339 (1979). It also radically transforms the Act. When "of the contractor" is given its ordinary meaning, the Act applies only to rights that federal contractors would otherwise hold, effectively expanding them by *giving away* any government title. Under Stanford's reading, however, the statute also *takes away* third-party rights, abrogating all state and federal laws regarding contract and patent ownership in the process. Such a broad effect would be worrisome even if required by the express terms of the statute; there is no reason to achieve that result by ignoring the statutory limitation ("of the contractor") that prevents it. *See Duncan*, 533 U.S. at 174 (the Court is "reluctant to treat statutory terms as surplusage in any setting" but is "especially unwilling to do so when the term occupies so pivotal a place in the statutory scheme" (internal quotation marks, citations, and alterations omitted)).[8]

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[8] In a footnote, Stanford suggests that the phrase "invention of the contractor" "excludes from the Act's coverage inventions created by third parties without the assistance of federal funding, where the contractor's employees had no role in its conception." Pet. Br. 32 n.11. If that is correct, it appears to concede this case, because (as the district court found) the invention was fully conceived at Cetus by October 1989, at which point no Bayh-Dole grants were involved. *See supra* pp. 6-7 & n.1. If Stanford means

2. "Retain"

The Act separately requires that all federal funding agreements allow contractors to "elect to retain title to any subject invention." 35 U.S.C. § 202(a). Of course, "'unless otherwise defined, words will be interpreted as taking their ordinary, contemporary common meaning.'" *Diamond* v. *Chakrabarty*, 447 U.S. 303, 308 (1980) (quoting *Perrin* v. *United States*, 444 U.S. 37, 42 (1979)). The common meaning of "retain" is "to keep hold or possession of" or "to continue having or keeping." *Oxford English Dictionary* 563 (1933); *accord Webster's New Collegiate Dictionary* 980 (1979) ("to keep in possession or use"); *American Heritage Dictionary* 1109 (1969) ("to keep or hold in one's possession"). The fact that the Act grants a right to "keep hold or possession" reinforces its limitation to inventions "of the contractor"—that is, inventions that the contractor already "hold[s] or possess[es]."

Stanford again rewrites the statute to suit its argument, introducing its first full quotation of Section 202(a) by recharacterizing the right to "retain title" as "the critical right to *take* title." Pet. Br. 12-13 (emphasis added). It also describes Section 202(a) as "vest[ing] new title in the contractor" (*id.* 36; *see also id.* 27, 33), "giving" or "granting" title (*id.* 1, 30, 36, 44), and allowing contractors to "obtain," "take," or "perfect" title (*id.* 12, 13, 21, 39). But "take" and "retain" are not synonymous: to "retain" means to *keep* in one's

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that Holodniy's status as its *employee* turns inventions conceived "without the assistance of federal funding" into "inventions of the contractor," then the contention is wrong because, as discussed in text, an employment relationship does not automatically vest the employer with ownership of employee inventions.

possession, whereas to "take"—like the other verbs Stanford prefers—means to "get into one's possession." *American Heritage Dictionary* 1311.[9]

3. The absence of "vesting" language

Congress's failure to refer to "vesting" is particularly noteworthy given that it expressly used such language in some—but not all—of the statutes that the Act replaced. *See* 42 U.S.C. §§ 2182 (inventions relating to nuclear material or atomic energy "shall be vested in, and be the property of, the [Atomic Energy] Commission"), 2457 (inventions made under performance of certain contracts with NASA "shall be the exclusive property of the United States"), 5908 (title to inventions made under contracts with Department of Energy "shall vest in the United States").

Those vesting statutes, which arise in specialized and sensitive areas, set forth unusual, reticulated procedures for patent issuance directly to the government. Two require any inventor working in the relevant *field* to file a special "statement under oath setting forth the full facts surrounding ... the invention or discovery ... and whether [it] was made or conceived" under a relevant contract. 42 U.S.C. §§ 2182, 2457(c). The agency must then be notified of the application and may "direct" that the patent issue directly to the agency if it believes that it was produced under a contract—a deci-

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[9] Elsewhere, Stanford proposes that "retain" be read as "synonymous with 'obtain'" (Pet. Br. 39) or "as a synonym for 'acquire' or 'receive'" (*id.* 37). While "obtain," "acquire," and "receive" are all synonyms for each other, none is a synonym for "retain." *New American Roget's College Thesaurus* 8 (1978) (acquire); *id.* at 425-426 (retain).

sion the inventor may appeal. *Id.* §§ 2182, 2457(d). The third provision likewise specifies that patents on covered inventions "shall be issued to the United States," subject to certain enumerated waiver procedures and considerations. *Id.* § 5908(a), (d)(1)-(11). These carefully-detailed procedures for vesting title in a party other than the inventor have no analogue in the Bayh-Dole Act, further indicating that the Act does not operate as a vesting statute.

The government, unlike Stanford, acknowledges that the Patent Act grants title "to the inventor, who may assign that right." U.S. Br. 16 (citing 35 U.S.C. §§ 101, 115, 116, 152). It contends, however, that that principle is displaced by 35 U.S.C. § 210(a), which provides that the Bayh-Dole Act "take[s] precedence over any other Act which would require a disposition of rights in subject inventions ... that is inconsistent with this chapter." *Id.* But Section 210(a) relates only to "subject inventions"—inventions "of the contractor" conceived or reduced to practice with the aid of federal funds. Thus, the "inconsistent" "disposition[s] of rights" over which the Bayh-Dole Act takes precedence are specific provisions—like those enumerated in Section 210(a)—that would allocate ownership of "invention[s] of the contractor" as between contractors and government agencies. The Senate Judiciary Committee thus explained that the Act "takes precedence over a number of statutory provisions that currently control to varying degrees the *patent policies of some agencies*"—not that it repealed generally-applicable Patent Act provisions governing ownership and assignment. S. Rep. No. 96-480, at 35 (1979) (Senate Report) (emphasis added).

This understanding of Section 210(a) is reinforced by its listing of 21 statutes, each of which is a specific

provision governing the relative ownership claims of the government and federal contractors with respect to sponsored inventions. *See* 35 U.S.C. § 210(a)(1)-(21). Not one is a general provision remotely similar to the Patent Act provisions dictating that title to inventions vests initially in inventors. The canon of *ejusdem generis*—like the plain text—thus suggests that the laws over which the Bayh-Dole Act takes precedence are those that create government claims to inventions "of the contractor," not general provisions of patent law that determine whether an invention is "of the contractor" in the first place. *See Hughey* v. *United States*, 495 U.S. 411, 419 (1990).

The government contends that *ejusdem generis* does not apply because "Section 210 does not provide 'a list of specific items followed by a general term.'" U.S. Br. 22 n.2 (citing *Hall St. Assocs.* v. *Mattel, Inc.*, 552 U.S. 576, 586 (2008)). That argument is hard to fathom; "any other Act" is a "general term," and the list of 21 preempted provisions is a "list of specific items." If the government is quibbling with the sequence, the objection is meritless; the canon limits a general term "in light of the specific terms that *surround* it." *Hughey*, 495 U.S. at 419 (emphasis added); *see also* 2A *Sutherland Statutory Construction* § 47:17, at 362-365 (7th ed. 2007) ("Where the opposite sequence is found, i.e., specific words following general ones, the doctrine is equally applicable[.]").

The government's reading of Section 210(a) also admits of no limiting principle. It is the Patent Act that prevents inventors from filing applications that fail to name every inventor, that name individuals who are not inventors, that claim inventive but unpatentable subject matter, or that claim an invention first conceived by another (even if not yet disclosed). 35 U.S.C.

§§ 101, 102, 116. Each of these provisions—and especially the last—could result in a "disposition of rights" in a federally-funded invention that is arguably "inconsistent" with a contractor's supposed right to take "perfect" title notwithstanding the otherwise valid claims of others. Yet the government presumably does not contend that the Bayh-Dole Act exempts federal contractors from those general patent-law principles.

In short, the text is plain. It grants contractors only the opportunity to "retain" rights to an "invention of the contractor"—rights that the contractor has obtained under other provisions of law—notwithstanding the fact that federal funding would otherwise give the government an interest in the invention. It does not "vest" title in a contractor or allow the contractor to "take" title from anyone.

B. Other Provisions In The Act And Related Regulations Confirm Its Limited Application

1. The Act's implementation through contract confirms its application to contractors, not third parties

Further confirmation that the Act does not alter third-party rights lies in Congress's judgment that the Act be implemented primarily through alterations in federal funding agreements between the government and its contractors. *See* 35 U.S.C. § 206 (directing implementation through "establish[ing the] standard funding agreement provisions required under this chapter"). Even the right to "elect to retain title" is subject to the terms of each particular agreement, which "may provide otherwise." *Id.* § 202(a). The contractor's responsibilities and the government's residual rights are imposed not by the statute directly, but by a direction that they be included in "[e]ach funding

agreement with a small business firm or nonprofit organization." *Id.* § 202(c)(1)-(8). In short, the Bayh-Dole Act regulates agreements between the government and funded entities; it does not affect the rights of strangers to such agreements.

Because the Act concerns contracts, the core regulation implementing the Act is a form *agreement* for use in federal research grants. 37 C.F.R. § 401.14. The language Stanford puts forward as allowing a contractor to retain "the entire right, title, and interest throughout the world to each subject invention" (Pet. Br. 43) appears in that form contract, not in a general interpretive regulation (37 C.F.R. § 401.14(a)). A bilateral contract is an appropriate vehicle for resolving ownership claims of two contracting parties; it cannot divest the rights of third parties not privy to the contract. *See Armstrong* v. *United States*, 364 U.S. 40, 45-46 (1960) (contract between government and federal contractor did not affect liens of persons "not parties to the contract").[10]

Moreover, in cases in which the government has taken title to an invention that a contractor failed to disclose, it has done so under these regulations *as they are embodied in the contract*, not through any self-executing force of the Bayh-Dole Act or the regulations themselves. *See, e.g., Campbell Plastics Eng'g & Mfg., Inc.* v. *Brownlee*, 389 F.3d 1243, 1247 (Fed. Cir. 2004)

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[10] Stanford's plea for *Chevron* deference (Pet. Br. 44), not raised below or in the petition for certiorari, is meritless. Nothing in the regulations suggests that the Department of Commerce's form agreement meant to address, much less abrogate, the rights of non-contracting third parties. The government's brief notably does not support Stanford's deference claim.

(interpreting right to retain in "Subsection 1.53 of Campbell Plastics's contract"); *see also Central Admixture Pharmacy Servs., Inc.* v. *Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347, 1352 n.4 (Fed. Cir. 2007) (government had discretionary right to take title based on "37 C.F.R. § 401.14, which was incorporated into the grant agreement between UC and NIH"); *Pilley* v. *United States*, 74 Fed. Cl. 489, 494-496 (2006) (contract between FAA and inventor gave government a "[l]icense under the [c]ontract" to subject inventions). In this respect, the Act's regulations resemble preexisting agency-specific regulations, which were "not self-executing" and "require[d] only the inclusion of the patent rights clause in the [agency]'s research contracts." *Mead Corp.* v. *United States*, 652 F.2d 1050, 1053 (D.C. Cir. 1981) (per curiam).

The only circumstance in which the Act envisions an actual taking of title to an invention is where a contractor *breaches* its obligations under a funding agreement, in which case the government may "receive title" from the breaching contractor. 35 U.S.C. § 202(c)(1)-(2); *Campbell Plastics*, 389 F.3d at 1249. The Act nowhere suggests that a contractor may simply take title from an innocent assignee like Cetus that did not even assume (let alone breach) any obligations to the government.

2. The Act's procedural protections, which follow its substantive scope, apply only to contractors

The Act is also notable in its concern for due process whenever the government seeks to limit a contractor's rights, even though contractors have *already* benefitted from government funding. *See, e.g.*, 35 U.S.C. § 203(b) (extensive appeal rights where gov-

ernment exercises "march-in rights"); *id.* § 202(b)(3) (same appeal rights when agency imposes exceptions on contractor's right to retain title). The implementing regulations further expand these protections (*e.g.*, 37 C.F.R. §§ 401.4, 401.6, 401.12) and grant even broader appeal rights regarding government determinations adverse to the contractor (*id.* § 401.11(b)).

The Act is even more careful about ensuring that the government not interfere with the contractor's rights to inventions that are funded privately or by educational awards like the one that paid Holodniy's salary while at Cetus. 35 U.S.C. § 202(f)(2) (agency can only require licensing of non-subject-inventions following agency adjudication subject to judicial review); *id.* § 212 (agency obtains no rights in inventions made under an award "primarily ... for educational purposes"); 37 C.F.R. § 401.1(a)(1) ("closely related [projects] fall[ing] outside the *planned and committed activities* of a government-funded project" are not covered by the Act (emphasis added)). If the government challenges a contractor's designation that a given project was privately funded and not subject to the Act, the contractor may appeal. 37 C.F.R. §§ 401.1(a)(1), 401.11(d).

In stark contrast, the Act contains not a single procedural protection for third parties that have neither sought nor received federal funds. The Act does not allow third parties to challenge the contractor's unilateral decision to designate discoveries as "subject inventions." Indeed, as happened here, a contractor need not even inform a private entity that might have a valid claim of ownership that the contractor has elected to "retain title." The failure to protect the rights of third parties is understandable in light of the Bayh-Dole Act's limitation to "inventions of the contractor": there is no need to protect third-party rights because the Act

affects only the rights of the government and the contractor. Stanford's reading of the Act, however, yields a situation in which Congress attended carefully to the property rights of contractors—who already benefit from government funding and can retain rights that otherwise might have been the government's—yet showed complete disregard for the property rights of third parties that received no federal funding and owed the government no obligation.

Treating the Bayh-Dole Act as a "vesting" statute is also highly problematic given how little a contractor need do to "retain" its rights beyond complying with obligations already in its funding agreement. Here, Stanford merely *averred* that the invention was federally funded, included that averment in its patent applications, and gave timely notice to the government. J.A. 42 ¶93. The district court required no further proof on summary judgment, notwithstanding Roche's objection that Stanford had failed to produce the relevant grant agreements or prove that they encompassed the claimed inventions. To this day, it remains unclear how the claimed inventions fall within the "planned and committed activities of a government-funded project." 37 C.F.R. § 401.1(a)(1).

If the Act applies only to rights that the contractor otherwise owns (but for any government interest), it makes sense to trust the contractor's averment, since the contractor gains nothing by subjecting its own privately-funded inventions to the requirements of the Act. But if, as Stanford asserts, the Act grants it *greater* rights to a federally-funded invention than Stanford would have to an invention funded from its private endowment—namely, by vesting Stanford with "perfect" title to inventions that it might otherwise share with private parties like Cetus—then the absence

of a requirement that the contractor prove a connection between the funding and the invention permits contractors to assert complete title to inventions based on nothing more than their own say-so. Indeed, that is precisely what Stanford did here.[11]

This Court should be reluctant to adopt an interpretation that allows federal contractors to divest third parties of intellectual property rights based solely on unilateral assertions of federal funding in patent applications and government disclosure forms. Nor should it lightly presume that Congress authorized such an outcome without any procedural protection for the third party—especially in a statute that, on its face, is highly protective of private property rights.

3. Federal regulations and university policies demonstrate that title initially vests in the inventor

Stanford attempts to read the Act against an "established practice of taking Government title to most federally funded inventions" (Pet. Br. 35), but in fact such practices were decidedly the exception. Stanford itself cites a case recognizing that the Department of Defense's pre-Bayh-Dole-Act contracting policy did

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[11] Roche appealed the district court's grant of summary judgment on this issue. *E.g.*, Roche C.A. Reply 15-16, 20-21. Taking the record in the light most favorable to Roche, as the district court was required to do, the evidence *at the very least* permits a reasonable jury to find that Stanford failed to show that the claimed inventions fell within the "planned and committed activities of a government-funded project." 37 C.F.R. § 401.1(a)(1). The Federal Circuit did not need to address this argument, but the material factual dispute remains an open issue here and on any possible remand.

"'not require that full title to the new inventions be assigned to the Government.'" *Mead Corp.* v. *United States*, 490 F. Supp. 405, 408 (D.D.C. 1980) (quoting Armed Services Procurement Regulations, 32 C.F.R. § 9-107.1(a) (1961)), *aff'd*, 652 F.2d 1050 (D.C. Cir. 1981). When the government did seek title, it typically did so through assignment. *See FilmTec*, 939 F.2d at 1571 (federal contract contained "warrant[y] that [the contractor] will obligate inventors to assign their rights" to the contractor, which in turn assigned its rights to the government).

The same is true with respect to inventions of federal employees. This Court ruled in 1933 that the government has no automatic title to its employees' inventions. *Dubilier*, 289 U.S. at 187-193. Under modern regulations and agency policies, there is likewise no automatic "vesting" of title except for unusual provisions that expressly use such language. *See supra* pp. 23-24. Rather, generally-applicable regulations contemplate that the government's interest in an invention may be "insufficient equitably to *justify a requirement of assignment to the Government* of the entire right, title and interest in and to such invention." 37 C.F.R. § 501.6(a)(2) (emphasis added). Government forms calling for the disclosure of inventions by employees thus allow the inventor-employee to *refuse* to assign the invention. *See, e.g.*, Air Force Form 1279 (Disclosure and Record of Invention), at 3 (allowing employee to answer "no" to the phrase "I agree to grant voluntarily to the Government the entire title to the invention"); Air Force Instruction 51-303 ¶7.1 (Sept. 1, 1998) (recognizing that an employee may "not agree to assign his or her entire right, title and interest in and to an invention to the Government"), *available at* http://www.af.mil/shared/media/epubs/AFI51-303.pdf. These provisions

likewise confirm that, when the government chooses to obtain title to employee inventions, it does so through the ordinary method of requiring the employee to execute an assignment.

The Bayh-Dole Act itself recognizes that title to federal employee inventions does not vest automatically in the government: it envisions that a federal agency "may" acquire an employee's invention. 35 U.S.C. § 202(e). Regulations implementing the Act are even plainer, providing that an agency "employing such co-inventor transfers or reassigns the right *it has acquired* in the subject invention *from its employee* to the contractor as authorized by 35 U.S.C. 202(e)." 37 C.F.R. § 401.10 (emphasis added). These provisions would be senseless under Stanford's "vesting" rule.

Section 202(e) defeats Stanford's argument in another way: it recognizes that title to a federally-funded invention may initially be *shared* among co-inventors employed by different entities, notably a contractor and a federal agency. In such a situation, Section 202(e) allows the agency to "consolidat[e] rights in the invention" in either the contractor or the agency. Again, that provision would make no sense if the Act presumptively vested "perfect" title in the contractor, since all rights would already be "consolidated" in the contractor (or, if the contractor elected not to "retain" its rights, in the government). But Section 202(e) makes perfect sense if the Act follows the ordinary rules of patent ownership: it allows the government to consolidate intellectual property rights that *initially vested in different co-inventors* under 35 U.S.C. § 101 and were subsequently assigned to the co-inventors' respective employers.

University practices—including Stanford's—also reflect the understanding that title to inventions, even federally-funded inventions, vests initially in the inventor, subject to assignment. *See, e.g.*, Pet. App. 119a (form agreement promising to assign to Stanford "such inventions as required by Contracts or Grants," including federal grants); Stanford Research Policy Handbook 5.1.1.A.1 (July 15, 1999) (title to "inventions conceived or first reduced to practice in whole or in part by members of the faculty or staff ... shall be assigned to the University, *regardless of the source of funding*, if any" (emphasis added)), *available at* http://rph.stanford.edu/5-1.html; University of Wisconsin Financial Administration Patent Policy III.A.9 (1985) ("[T]he laws permit a university itself to accept assignment" of subject inventions under the Bayh-Dole Act, and the university must designate an office or organization that "will accept assignment of the invention"), *available at* http://www.uwsa.edu/fadmin/gapp/gapp34.htm; Iowa State University Intellectual Property Handbook 27 ("employees will be required to assign ownership" to the university where, *inter alia*, intellectual property "was funded in whole or in part by any agency of the federal government"), *available at* http://www.techtransfer.iastate.edu/documents/filelibrary/images/pdf/IP_Handbook_081104162623.pdf (last visited Jan. 24, 2011).

Stanford's claim to a vesting of "perfect" title is also refuted by its own practices. The public record discloses several instances in which Stanford collaborated with *Cetus co-inventors* on federally-funded inventions, after which the Cetus co-inventors assigned

their rights to Cetus.[12] Stanford also shares ownership with other private entities of numerous patents governed by the Bayh-Dole Act.[13] Even with respect to the patents at issue in this case, Stanford did not treat the invention as vesting directly in Stanford. Rather, it did what it always does: it sought assignments from the named co-inventors. J.A. 42.[14] None of these actions would make sense if the Bayh-Dole Act "vested" universities with "perfect" title.

Accordingly, Stanford's university *amici* (unlike Stanford itself) concede that the Act does not displace the rights of private co-inventors who are not "conducting research under a federal funding agreement." AAU Br. 23. That concession is irreconcilable with Stan-

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[12] *Biogen, Inc.* v. *Berlex Labs., Inc.*, 318 F.3d 1132, 1133 (Fed. Cir. 2003) ("The inventors are Francis P. McCormick and Michael A. Innis of Cetus Corporation, and Gordon M. Ringold of Stanford University. Berlex acquired the Cetus rights in 1991."); *see also, e.g.*, U.S. Patents Nos. 4,684,623, 4,764,465 (listing Cetus and Stanford as assignees of inventions made using government funds).

[13] *See, e.g.*, U.S. Patent Nos. 7,778,386 (co-assigned to General Electric), 6,156,878 (co-assigned to Becton Dickinson).

[14] The same is true of the patents listed in notes 12 & 13 above: Stanford obtained assignments, recorded them in the Patent Office, and prosecuted the patent applications as an assignee of the inventors' rights. When Stanford licensed the claimed invention to the government, it did so only in the name of the co-inventor(s) who assigned to Stanford, not the co-inventors who assigned to a private third party. *Compare, e.g.*, U.S. Patent No. 7,778,386 (identifying four co-inventors, three of whom assigned their interests to General Electric) *with* Stanford's License to NIH of U.S. Patent No. 7,778,386 (listing only the one co-inventor who assigned his interests to Stanford). Respondents will request leave to lodge the relevant license and assignment documents under Rule 32(3).

ford's argument that the Act "vests" perfect title to all federally-funded inventions in the contractor. It also suffices to affirm the judgment here because, when the invention was conceived at (and transferred to) Cetus, Holodniy was not "conducting research under a federal funding agreement" subject to the Act, even according to Stanford itself. *See supra* pp. 6-7 & n.1.[15]

4. Stanford's efforts to read the Act as a vesting statute fail

Stanford proposes three reasons for reading the Act as applying beyond "inventions of the contractor." None is persuasive.

First, Stanford suggests (Pet. Br. 33-34) that because "th[e] right to retain title is conditioned on compliance with precisely defined procedural requirements," the absence of other "prerequisites to securing title" can be inferred under *expressio unius*. Not so. The Act enumerates "precisely defined procedural requirements" for *retaining* title, permitting the inference that there are no other requirements for *retaining* title. But that simply begs the question what it means to "retain title," a question not answered by replacing "retain" with "secur[e]." Pet. Br. 34. Just as Rule 23's

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[15] AAU's attempt to argue that this case proceeds "on the premise" that the invention was conceived after 1989 (AAU Br. 18) fails. Although the Federal Circuit believed that the terms of the VCA would have applied to inventions conceived after Holodniy left Cetus (Pet. App. 15a), it did not disturb the district court's finding that the invention was "conceived during Holodniy's consultancy at Cetus" (*id.* 58a). AAU's effort to relitigate the timing of conception is particularly inappropriate given Stanford's refusal to state when *it* believed the invention was conceived. *See* Pet. App. 58a n.7.

enumeration of precise requirements for maintaining a class action does not exempt a class plaintiff from compliance with the other Rules of Civil Procedure, the Bayh-Dole Act's enumeration of procedures to "retain" rights does not exempt a federal contractor from the ordinary steps required for obtaining whatever rights it wishes to "retain."

Second, Stanford suggests that because other sections of the Bayh-Dole Act use the words "acquire" and "receive," the right to retain in Section 202(a) should also be understood as a right to "acquire" or "receive" title. Pet. Br. 36. But ordinary canons of construction *discourage* attributing the same meaning to different phrases in different parts of the same statute. *See Barnhart* v. *Sigmon Coal Co.*, 534 U.S. 438, 454 (2002). Moreover, the other provisions extend beyond retention of title under Section 202(a). For instance, Section 203(a)'s provision that the government may "march-in" (*i.e.*, compel licensing) applies not only where rights have been "retained" under Section 202(a), but also where a contractor receives an assignment of an invention from a government co-inventor (§ 202(e)) or where, as Section 203(a) itself suggests, a small business or nonprofit is the "assignee or exclusive licensee of a subject invention." Section 203(a)'s reference to "acquir[ing] title under this chapter" thus ensures that the government's march-in rights apply in each situation.

Stanford's reliance on Section 204 (Pet. Br. 36) is similarly misplaced. Section 204 requires small businesses and nonprofits that "receive[]" title to a subject invention to employ U.S. industry in commercializing it. That provision applies even more broadly than Section 203(a) to subject inventions "receive[d]" in *any* way, not just "under this chapter" and certainly not just through retention under Section 202(a). Thus, rights

received through assignment, constructive trust, corporate succession, bankruptcy, bequest, or other means are still subject to the requirements of Section 204 if "receive[d]" by a nonprofit or small business. The use of a broader term is thus natural and meaningful and in no way suggests that a right to "retain" title to an "invention of the contractor" means anything other than what it says. *See Connecticut Nat'l Bank* v. *Germain*, 503 U.S. 249, 253-254 (1992) (the "cardinal canon" of statutory interpretation is "that a legislature says in a statute what it means and means in a statute what it says there").

Third, Stanford argues that the contractor's right to "retain title" must really be a right to "take title" because Section 202(d) supposedly places inventors at the "back of the line" when it comes to ownership rights. Once again, however, Stanford ignores both the text and context of the statute. Section 202(d) does place inventors at the back of the line, but only as to inventions "of the contractor," *i.e.*, inventions that have *already been assigned* by the inventor to the contractor pursuant to established principles, most likely under a patent policy or an employment agreement that effectuates such an assignment. *See supra* p. 34. Section 202(d) nowhere suggests that the Act governs the rights of inventors as to inventions that have not become inventions "of the contractor." *See, e.g.*, *Fenn* v. *Yale Univ.*, 393 F. Supp. 2d 133, 141-142 (D. Conn. 2004) ("[T]he primary purpose of the Bayh-Dole Act is to regulate relationships of small business and nonprofit grantees with the Government, not between grantees and the inventors who work for them.").

Section 202(d) simply provides that the government may, on occasion, allow an inventor to retain title after the contractor-assignee has disclaimed its rights.

Section 202(d) governs the rather ordinary case in which a contractor is uninterested in an invention and so allows the rights it obtained to revert to the assigning inventor-employee—a result contemplated by Stanford's own policies. *See* Stanford Research Policy Handbook 5.1.1.A.4 ("If the University cannot, or decides not to, proceed in a timely manner to patent and/or license an invention, it may *reassign ownership* to the inventors upon request to the extent possible under the terms of any agreements that supported or related to the work." (emphasis added)). The provision requiring the sharing of royalties with inventors (35 U.S.C. § 202(c)(7)(B)) is similarly understandable in the context of "inventions of the contractor," as to which the inventor has already assigned away his ownership right and, *a fortiori*, his right to a royalty; Section 202(c)(7)(B) restores that right in part.

C. Legislative History Does Not Help Stanford

Because neither the statutory text nor the facts of this case support its desired outcome, Stanford devotes fully one-fifth of its brief to legislative history. Pet. Br. 2-10, 38-42. But neither Stanford nor its *amici* identify a single statement addressing third-party rights, let alone suggesting that the Act automatically divests them. The lesson from this history is simple: Congress intended no such result.

The legislative record repeatedly voices concern over the "ineffective patent policies" of *government agencies*, which together created a complicated jumble of statutes, regulations, and "reams of unnecessary bureaucratic redtape." Senate Report 2, 21. Congress responded with "a uniform patent policy" that would "apply to all agencies." *Id.* 15; *see also id.* 16, 26. In Stanford's words, the legislative record "ma[kes] clear

that *the Government* would 'relinquish patent rights that would encourage and stimulate private industry to develop discoveries into products available to the public.'" Pet. Br. 39 (quoting 126 Cong. Rec. 1796 (1980) (statement of Sen. Bayh)) (emphasis added).

The Act accordingly limited the circumstances in which *the government* claimed rights in inventions that otherwise belonged to the contractor. By "reduc[ing] Government interference," Congress aimed to foster greater public/private cooperation. 126 Cong. Rec. 1992 (statement of Sen. Dole) (internal quotation marks omitted); *see also id.* 29,895 (statement of Rep. Kastenmeier), 30,364 (statement of Sen. Bayh), 30,365-30,366 (statement of Sen. Dole); Senate Report 22, 24, 29-30. Those in favor of the Act endeavored to turn an "adversarial" relationship between government and contractor into a productive, cooperative one. 126 Cong. Rec. 1992 (statement of Sen. Dole). Opponents saw it as a "radical, far-reaching giveaway[]" of public property to private entities. *Id.* 8739 (statement of Sen. Long); *accord* H.R. Rep. No. 96-1307, at 29 (1980) (dissenting views of Rep. Brooks). But no legislator suggested that the statute would affect the ordinary laws of ownership and assignment that determine the rights of third parties not receiving government funds.[16]

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[16] Stanford cites a statement by Senator Kennedy that nowhere indicates a belief that small businesses and universities need "undivided" or "indisputable" title as against other *private* entities to secure venture capital. 126 Cong. Rec. 1799 (cited at Pet. Br. 52). Rather, like all other legislators who commented on the Act, Senator Kennedy focused on the benefits of giving small businesses and universities increased rights as against the *government*. *Id.*

Thus, while some legislative materials contain broad language referring to "automatically grant[ing] small businesses and nonprofits title to inventions" (Senate Report 36), there is no basis to conclude that such statements were made with an eye toward the scenario presented by this case. Rather, Congress's concern was for inventions that already otherwise belonged to the contractor. Indeed, the Senate Report's section-by-section analysis clarifies that, under Section 202(a), funded entities may elect "ownership of *their inventions*," *i.e.*, inventions "of the contractor." Senate Report 31 (emphasis added).

Stanford may be correct that "[n]o Senator in favor of S. 414 suggested that an assignment from the inventor was necessary for universities and small businesses to 'retain' patent rights" (Pet. Br. 39), but the point is that no legislator mentioned inventor assignments *at all*. If any inference can be drawn from this silence, it is that no legislator saw a need to reassert a basic point of law that nobody proposed to change. Rather, the legislation addressed solely whether the contractor could "retain" rights *already obtained* against claims by the federal government.

Relying on written testimony from a single witness from the National Science Foundation, the government asserts that, under the preexisting regime, "[a]n institution's failure to obtain an effective assignment of rights from the researcher ... could compromise the allocation of rights and obligations under [an Institutional Patent Agreement (IPA)]" and that "Congress enacted the Bayh-Dole Act to address these shortcomings." U.S. Br. 4-5. The testimony does not support the government's argument. The NSF witness testified that "NSF has negotiated recoupment agreements in a limited number of instances when patent rights were left

with an individual inventor rather than a grantee institution." *Government Patent Policy Act of 1980: Hearing on H.R. 5715 Before the Subcomm. on Science, Research and Technology of the H. Comm. on Science and Technology*, 96th Cong., 2d Sess. 80 (1980). The witness did not explain why patent rights "were left with an individual inventor" or that the witness (to say nothing of Congress) even viewed that as problematic, let alone a "shortcoming" in the pre-Bayh-Dole regime that the Act was intended to cure. One ambiguous statement by one witness before one subcommittee of one Chamber of Congress in no way suggests that Congress as a whole intended fundamentally to recast the rules of patent ownership. *See Regan* v. *Wald*, 468 U.S. 222, 237 (1984).

In fact, the Bayh-Dole Act incorporated many aspects of the IPA regime because, as Senator Bayh makes clear (Bayh Br. 7), "[t]he IPA programs proved extremely successful." The form agreement for federal grants under the Act is strikingly similar to IPA clauses that obligated grantees to require non-clerical workers "promptly [to] report and assign all subject inventions." Federal Council for Science and Technology, *Report on Government Patent Policy* 330-332, 342-343 (1976); *cf.* 37 C.F.R. § 401.14(f)(2) (obliging contractors to "require, by written agreement, ... employees, other than clerical and nontechnical employees, to ... execute all papers necessary to file patent applications on subject inventions and to establish the government's rights"). There is no reason to presume, as the government does, that Congress viewed inventor assignments as a problem with the IPA system, rather than part of a "successful" program that the Act took as accepted background in crafting a strikingly similar system. Bayh Br. 7; AIPLA Br. 7-18. The rational infer-

ence is that, to the extent Congress was aware of the requirement for inventor assignments to contractors, it left that requirement in place.

In the end, as another of Stanford's *amici* admits, the issues that Stanford raises here are simply "different" from those that "existed in the pre-Bayh-Dole regime": namely, "whether the Government, on the one hand, or the federally funded contractor, on the other hand, would ultimately obtain title to the invention." BayhDole25 Br. 7. Congress addressed *that* concern by creating a framework for settling the respective rights of government and contractor. Nothing in the Act or its legislative history suggests that Congress sought to address the "different" issue of third-party rights obtained through inventor assignment.

D. Stanford's Position Raises Serious Constitutional Questions The Court Should Avoid

The constitutional avoidance canon provides another reason to reject Stanford's attempt to rewrite the Act. "If one of [two plausible constructions] would raise a multitude of constitutional problems, the other should prevail." *Clark* v. *Martinez*, 543 U.S. 371, 380-381 (2005). This rule rests upon the "reasonable presumption that Congress did not intend the alternative which raises serious constitutional doubts," and it is properly invoked to avoid consideration of the constitutional question. *Id.* at 381. Stanford's reading of the Bayh-Dole Act raises two related and substantial constitutional questions: (1) whether the Act works an uncompensated taking; and (2) whether the Act provides sufficient process to ensure that no such taking occurs.

The takings problem raised by a right to "take title" is manifest. "The government has no more power

to appropriate a man's property invested in a patent than it has to take his property invested in real estate; nor does the mere fact that an inventor is, at the time of his invention, in the employ of the government transfer to it any title to or interest therein." *Solomons* v. *United States*, 137 U.S. 342, 346 (1890). Thus, as in the case of a federal employee, the mere fact that some federal funding is involved does not allow the government to divest a third party of its otherwise valid right to an invention, much less transfer it to a different private party.

The facts of this case demonstrate the seriousness of the constitutional problem. Cetus gave Holodniy valuable scientific expertise and proprietary materials in exchange for an assignment of any resulting invention. When the claimed invention was conceived in October 1989, the settled effect of the VCA was to pass title to Cetus. Pet. App. 18a, 59a. Had nothing else occurred, there would be no question as to Cetus's and Roche's right to practice the invention. Stanford's argument—that a federal statute transforms what was validly owned by Cetus one day into a possession of Stanford's the next, without any compensation to Cetus—is the essence of a takings violation. *See Eastern Enters.* v. *Apfel*, 524 U.S. 498, 523 (1998) ("'It is against all reason and justice' to presume that the legislature has been entrusted with the power to enact 'a law that takes *property* from A. and gives it to B[.]'" (quoting *Calder* v. *Bull*, 3 U.S. (3 Dall.) 386, 388 (1798) (Chase, J.))).

It is no answer to say, as the government does, that the property never belonged to Cetus because Holodniy could only transfer a contingent right. U.S. Br. 19. In October 1989, by which time the invention was conceived and assigned to Cetus (Pet. App. 57a-58a), it

could not have been a "subject invention" under any reading of the Act because it had not been "conceived or first actually reduced to practice *in the performance of work under a funding agreement*" (35 U.S.C. § 201(e) (emphasis added)). Rather, all the work was done at Cetus without use of Bayh-Dole grants. To say that Cetus's title at that time was "contingent" on whether Stanford *subsequently* used federal funds in clinical trials and *even later* made a Bayh-Dole election simply reinforces the constitutional difficulty of a retroactive divestiture of private property through Stanford's discretionary acts.

Perhaps recognizing this unacceptable consequence of its argument, Stanford asserts, in very careful phrasing, that Holodniy worked on "the federally funded research" before going to Cetus. Pet. Br. 17. But it cites no evidence of work on *the inventions at issue* before Holodniy arrived at Cetus, and there is none. In fact, Holodniy admitted that he only began working on the invention in September 1989 (Supp. J.A. 15) and that he had no experience "in th[e] field" of PCR-based quantitation before arriving at Cetus (J.A. 57). Below, Stanford insisted that federally-funded inventive work did not begin until July 1990. *See supra* pp. 6-7 & n.1. The government, for its part, takes no position on *when* Holodniy performed work funded by the "two federal grants." U.S. Br. 17.

Because there is no evidence of any federally funded work until after the invention was conceived, nor of the amount of such funding, Stanford's position must be that use of even $1 of federal funding in reducing an invention to practice would work a retroactive confiscation of intellectual property conceived entirely using private funds and already assigned to a third party for valuable consideration. *See* Pet. 12 (arguing

that the Act applies to inventions "conceived earlier without using government funding" but "later reduced to practice ... using government funding"); Pet. Br. 32 ("[T]he quantity of federal funding is not dispositive."). That outcome, threatened here, is at least constitutionally questionable.

Stanford's reading also raises a serious question regarding due process, because it provides no means for a third party to challenge the contractor's election. The Act envisions no notice to a third-party assignee—even if the contractor knows that the assignee exists, as Stanford's agents Merigan, Holodniy, and Katzenstein knew of Cetus. Nor does it provide an opportunity to argue that an invention is not a "subject invention" covered by the Act. These questions are easily avoided by reading the statute to mean what it says: it grants contractors a right to "retain" inventions "of the contractor," not a right to "take title" to inventions that belong to someone else under the ordinary rules of patent ownership.

E. Stanford's Policy Arguments Miss The Mark

Stanford and its *amici* extol the wisdom of the Bayh-Dole Act at length, and Roche readily agrees. The pre-1980 system *was* ill-conceived: the government often ended up with rights to inventions it had neither the incentive nor the means to commercialize. The Bayh-Dole Act remedied that situation by extracting the government from the system almost entirely. *See* Pet. Br. 9 (Act addressed the problem that "patents gathered dust on *Government shelves*" (emphasis added)); U.S. Br. 25 (Congress viewed universities as "better positioned *than the federal agencies* to develop federally funded inventions" (emphasis added)).

Stanford goes astray, however, in suggesting that abrogating *third-party* ownership rights would advance Congress's policies. Of course, even if Stanford's policy arguments were well-taken, the Act must be limited to the scope that Congress gave it. But Stanford's arguments are not well-taken. The American system of intellectual property ownership functions smoothly under long-established rules of ownership and assignment, which apply whether an invention is federally-funded or not. The Court should refuse Stanford's effort to knock down and rebuild that system at its foundations based on a rule of "vesting."

1. Inventions, both federally-funded and not, are successfully commercialized without divesting third parties of their intellectual property

Stanford and its *amici* argue that, unless they prevail, commercialization of innovative products will be impeded by the hypothetical risk "that an inventor, at some point, may have inadvertently or intentionally entered into an undisclosed agreement with an unknown third party." Pet. Br. 46; *see also* U.S. Br. 30; AAU Br. 34. Stanford forgets that such risks are not unique to federal contractors, yet private investment in innovation continues apace, accounting for the bulk of the investment in research and development in this country. *See* National Science Board, Science and Engineering Indicators 2010, at 4-4 & 4-14 (2010) ("The business sector itself provided an estimated $268 billion of funding for R&D in 2008, or 67% of the U.S. total."). That economic activity rests not on any special vesting statute or on disregarding settled rules of contract and patent law, but rather on enforcing them. AIPLA Br. 29-30.

Stanford's argument also rings hollow in light of the Act's undisputed success notwithstanding the common understanding that it does not affect rights of parties other than the government and federal contractors. *See, e.g.*, *Fenn*, 393 F. Supp. 2d at 141-142. Universities have thus designed their patent policies on the assumption that inventions—even federally-funded inventions—vest in the inventor and must be assigned to the university in writing. *See supra* p. 34. And universities know how to obtain effective assignments of their employees' future, as-yet-unconceived inventions. *E.g.*, MIT Patent Policy (Apr. 14, 2010), *available at* http://web.mit.edu/tlo/www/downloads/doc/IPIA.doc ("I will disclose promptly to and assign to, and I hereby assign to, M.I.T. all rights to all inventions ... conceived, invented, reduced to practice, or authored by me, either solely or jointly with others."); Cal. Inst. of Tech. Patent & Copyright Agreement (Dec. 30, 2003) ("I agree to assign, and hereby do assign, to the Institute all such inventions and copyrightable material[.]"), *available at* https://www.ogc.caltech.edu/Forms/documents/patentagreement. That Stanford failed to do so here does not suggest that the system is fraught with uncertainty. On the contrary, it shows that universities are in firm control of their assignment policies. Their incentive to write effective contracts, combined with researchers' incentive to deal cautiously with their employers, has produced virtually no litigation of this type in 30 years of experience under the Act. The Act's continued success is not contingent on the Court rewriting it now.[17]

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[17] It is hard to know what to make of AAU's protest that, "if Roche's advice is followed" and universities obtain effective as-

Indeed, the fear of secret assignments dating back "years" (Pet. Br. 28; U.S. Br. 30) has long been addressed—for privately-funded and federally-funded inventions—by 35 U.S.C. § 261, which voids unrecorded assignments as against subsequent bona fide purchasers. Accordingly, even if a university cannot secure an effective assignment in advance, it can protect itself against any unknown and ancient assignments by recording a subsequent assignment for value. This rule functions perfectly well in private settings to provide the certainty of title necessary for licensing and commercialization. Stanford cites no reason why federally-funded inventions require a different regime.

Of course, Section 261 does not protect Stanford here because, as both courts below correctly held, Stanford had notice of Holodniy's assignment, which he signed within the scope of his employment after being sent to Cetus by Merigan to do Stanford's business. Pet. App. 17a, 63a-64a. Stanford's hypotheticals (*e.g.*, Pet. Br. 46-47) are equitably compelling precisely because they lack this feature. This Court has not granted certiorari to review this state-law holding of notice, which is in any event consistent with federal law and reflects the application of standard agency principles. *Curtis, Collins & Holbrook Co.* v. *United States*, 262 U.S. 215, 222-223 (1923).

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signments from their employees, then "the next case with facts like this one" could be resolved in the university's favor. AAU Br. 35. AAU seems to be bemoaning the fact that contractual language matters. It is in no way "opportunism" or lacking in "principle" (*id.*) to insist that contracts like the VCA and statutes like the Bayh-Dole Act be enforced according to their terms, while recognizing that a different case with different contracts might yield a different result.

Ultimately, Stanford's primary objection appears to be that it does not trust its own employees. But *every* employer runs the risk that an employee's actions may have undesired consequences. Nothing in the legislative history suggests that Congress sought to treat employees of federal contractors like children or thieves or to relieve contractors of the ordinary consequences of their agents' actions. Employers protect against such risks through employment contracts or, if need be, through suits for breach of fiduciary duty, unjust enrichment, or other tort or equitable claims. At least two universities have brought such claims against former researchers. *See St. John's Univ.* v. *Bolton*, 2010 WL 5093347, *40-41 (E.D.N.Y. Dec. 10, 2010) (denying motion to dismiss university's contract and tort claims against former researchers); *Fenn* v. *Yale Univ.*, 2005 WL 327138, *6 (D. Conn. Feb. 8, 2005) (ruling that former faculty member obtained a patent "through fraud, civil theft, and breach of fiduciary duty" and ordering him to reassign the patent to Yale); AIPLA Br. 29.

2. Stanford's reading would chill innovative collaboration and commercialization of inventions

Rather than creating certainty, Stanford's position would foster uncertainty by creating a highly unusual and unpredictable exception to ordinary ownership rules. Under Stanford's reading, any collaboration will raise a risk of loss of intellectual property rights if, unbeknownst to one collaborator, the other makes use of even a modicum of federal funds. The likely result would be that companies that were dissuaded from collaborating under the pre-Bayh-Dole regime due to fear that the *government* would take their intellectual prop-

erty will be similarly dissuaded by the identical fear that *universities* will do so. *See* Senate Report 21 (reporting that companies "are reluctant to use university research facilities because they fear that any resulting patent rights will be 'tainted' if the university is also receiving Federal support in related research").

Stanford suggests that Cetus could have protected itself had it "approach[ed] Stanford" about the matter (Pet. Br. 53 n.21) rather than relying on Stanford's agent Holodniy. But it is not clear that any agreement from Stanford would have protected Cetus under Stanford's view of the law, in which contracts are swept away by force of a federal "vesting" statute that *forbids* universities from making assignments without government approval. *See* 35 U.S.C. § 202(c)(7)(A). It is hard to envision what contractual assurance would survive Stanford's all-consuming vision of the Bayh-Dole Act. Stanford's position would thus chill collaboration between industry and academy for fear of an unavoidable retroactive divestiture of intellectual property.

Moreover, contrary to Stanford's assertion, there is no "certainty" to be had from a rule that automatically vests title to employee inventions in the contractor. Instead, the uncertainty would surface in questions about individual inventors' employment status, a state-law question with easily as many "vagaries" as the "private contract law" Stanford derides. Pet. Br. 55. In California, employee status turns on a non-exhaustive eleven-factor test; written agreements are not determinative. *See S.G. Borello & Sons, Inc.* v. *Department of Indus. Relations*, 769 P.2d 399, 403-405 (Cal. 1989). Thus, one could not predict with "certainty" how Stanford's "vesting" rule would apply to research by undergraduates, graduate students, faculty on sabbatical or leave of absence, volunteer researchers

with day jobs elsewhere, or university employees with outside employment or consulting arrangements. *See, e.g., University of Pittsburgh* v. *Townsend*, 2007 WL 2263079, *2, 20 (E.D. Tenn. Aug. 3, 2007) (ruling that assignment in inventor's consulting agreements, not the Bayh-Dole Act, governed patent ownership), *aff'd*, 542 F.3d 513 (6th Cir. 2008).

Finally, as this case demonstrates, depriving a third party of its valid rights to practice an assigned invention would burden commercialization of innovative products. Stanford filed its parent application in May 1992, but apparently took no steps to commercialize the claimed inventions for the following eight years. There is no evidence that Stanford attempted to partner with private producers, raise venture capital, or license the invention. Roche, by contrast, developed, obtained FDA approval for, and commercialized a product that has helped millions of HIV patients and has been used in numerous U.S. hospitals and clinics—including Stanford University Hospital. In 2000, when Stanford threatened legal action if Roche continued to make and sell its products, Roche had already invested heavily in the product, creating manufacturing and distribution jobs in this country. Congress did not enact the Bayh-Dole Act to create a new class of non-practicing entities to tax commercial development by American industry and increase expenses to patients and the health-care system.

3. The government's rights are protected

Stanford also suggests that the contractor must obtain clear, certain, and perfect title in order to protect the government's rights. Pet. Br. 48-54. But the government's expectations arising from federal grants are protected in the exact way expectations are always

protected when one party pays another for certain promises—*by contract*. The Bayh-Dole Act ensures that the government's rights are protected through provisions in a funding agreement that are the *quid* for the federal grant *quo*. The Act does not impose obligations or responsibilities—much less forfeiture of intellectual property rights—on strangers to that agreement.

Accordingly, under the heading "Contractor Action to Protect the Government's Interest," the form contract in the Act's implementing regulations contains an express promise by the contractor

> to execute or to have executed and promptly deliver to the Federal agency all instruments necessary to (i) establish or confirm the rights the Government has throughout the world in those subject inventions to which the contractor elects to retain title, and (ii) convey title to the Federal agency when requested ... and to enable the government to obtain patent protection throughout the world in that subject invention.

37 C.F.R. § 401.14(f)(1). The contract also contains related obligations regarding contractor employees, including a promise that the contractor "require, by written agreement, its employees ... to execute all papers necessary to file patent applications on subject inventions and to establish the government's rights in the subject inventions." *Id.* § 401.14(f)(2). NIH guidance for grant recipients specifically directs grantees to "review existing agreements with third parties and revise them, as appropriate, to ensure they are consistent with the terms and conditions of their NIH grant awards." NIH Grants Policy Statement ¶8.2.4, *avail-*

able at http://grants.nih.gov/grants/policy/nihgps_2010/nihgps_ch8.htm#_Toc271264954.

The possibility that a contractor might fail to secure exclusive rights to an invention is no different from other possible actions by which a contractor might deprive the government of patent rights, including failure "to continue the prosecution of a patent application, pay maintenance fees, or defend in a reexamination or opposition proceeding on a patent," without telling the government. 37 C.F.R. § 401.14(f)(3). A contractor could also deprive the government of its rights by publishing the invention and failing to file a timely patent application. 35 U.S.C. § 102(b). In any such case, the remedy is not to reincarnate the patent that the contractor failed to secure, but for the government to sue for breach of contract including, if appropriate, reclaiming the amount funded to put the taxpayers in the same position they would have occupied had no funding been granted at all.

Of course, these issues are not presented here. Stanford retains the title it obtained from Merigan and Katzenstein, has delivered a paid-up license to the government, and remains an available target for march-in rights. Contrary to Stanford's unsupported assertion, Roche cannot prevent Stanford from "licensing to other parties" (Pet. Br. 46); Stanford and the government can use and license the claimed inventions without accounting to Roche. 35 U.S.C. § 262. This provides only greater reason to prefer contract remedies to the "vesting" of "perfect" title in the contractor—in some cases, such as this one, vesting of title in the contractor would create no advantage for the public or government whatsoever.

II. Stanford's Other Arguments Are Not Properly Before The Court And Lack Merit

Stanford closes with two arguments on which it did not seek certiorari and that are accordingly not before this Court. *Riegel* v. *Medtronic, Inc.*, 552 U.S. 312, 330 (2008). They lack merit in any event.

1. Stanford argues that the Bayh-Dole Act should be presumed to impose a status "analogous to the 'hired to invent' doctrine" on all Stanford employees—a status that, Stanford suggests, "vests [title] as an original matter in the employer." Pet. Br. 57. This argument both misunderstands and misapplies the "hired to invent" doctrine.

First, as demonstrated by the very case Stanford cites, the "hired to invent" doctrine follows ordinary patent principles and vests title in the *inventor*, subject to an assignment. In *Standard Parts*, the question was whether the Court should require the inventor to "*assign and transfer* to the company the legal title to the letters patent" based on the inventor's employment contract. 264 U.S. at 59 (emphasis added). After reviewing the terms of employment, the Court held that such an assignment was required because "the invention of a specific thing ... was the object and effect of Peck's contract." *Id.* at 57. The Court thus ruled only that the inventor was obliged to assign the title he was still holding to his employer; it neither suggested that title "vests as an original matter in the employer" nor determined the effect on any otherwise valid assignment to a third party.

Second, the "hired to invent" doctrine is only a default rule about the interpretation of employment contracts that contain no express terms regarding assignments of intellectual property. Accordingly, the out-

come can vary considerably based on the specific employment relationship. *See, e.g.*, *Hapgood*, 119 U.S. at 229, 233 (even employee who agreed to "devote his time and services to devising improvements in, and getting up and perfecting, plows adapted to the general trade of the corporation" was not obligated to assign the invention to his employer). It makes no sense to apply the doctrine where—as here—the disposition of intellectual property is the subject of express agreements among the relevant parties. And in any event, the government's contracts *with its own employees* do not vest title automatically in their employing agency. *See supra* pp. 31-33. Stanford does not explain why "unique federal interests" would impose a different rule on those supposedly "hired to invent" by Stanford compared to those supposedly "hired to invent" by the government itself.

2. Stanford also invokes "equities," suggesting that Roche "slept" on its rights and that there are "questions about the enforceability" of Holodniy's VCA. Pet. Br. 59. Any enforceability questions were resolved when both courts below rejected Stanford's arguments under California law. Pet. App. 21a-22a, 54a-58a. And the "equities" of this case do not favor Stanford.

When Holodniy arrived at Cetus, he had—by his own admission—no skill whatsoever in the art of PCR. His development of the PCR-based HIV assay that constitutes his primary inventive contribution and that lies at the heart of the patents-in-suit relied crucially on the expertise of Cetus scientists and Cetus's proprietary materials. In exchange, Holodniy signed the VCA in his capacity as an employee and agent of Stanford, giving Stanford notice thereof under California law. Nonetheless, when Stanford elected to claim title to the inventions for itself, it did not so much as notify Cetus;

its first notice of reliance on the Bayh-Dole Act was at summary judgment in this infringement suit. *See supra* pp. 3-8, 11-12.

Although Roche (unlike Stanford) did not seek a patent monopoly, it did not sleep on its rights. To the contrary, Roche has commercialized PCR-based HIV testing kits for fifteen years in the open market. It is hard to see anything "equitable" in the argument that a university may "take title" from—and then sue for infringement—a company that critically contributed to an invention, obtained an otherwise valid assignment of rights from the university's agent, and then designed, manufactured, and distributed a product advancing medical treatment for many ailing Americans.

CONCLUSION

The judgment of the court of appeals should be affirmed.

Respectfully submitted.

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REPLY BRIEF

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BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.,

Respondents.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

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CORPORATE DISCLOSURE STATEMENT

The corporate disclosure statement included in the Petitioner's opening brief, pursuant to Supreme Court Rule 26.1, remains accurate.

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REPLY

This case requires the Court to decide whether a university receiving federal research funding secures clear title to resulting inventions of its employees when it fully complies with the requirements of the Bayh-Dole Act, 35 U.S.C. §§ 200-212. The court below held otherwise, ruling that one of Stanford's employee-inventors, whose work was always funded by NIH grants, could nonetheless assign away his rights and thereby require Stanford to share title with his assignee. That decision is wrong because the statute's language and context show that it comprehensively defines the ownership interests of contractors, inventors, and the Government, and gave Stanford a conditional right to title that its employee could not assign away to a third party.

Roche answers this showing on two levels. First, contrary to the Act's title and express language, it argues that the Bayh-Dole Act does not actually govern the disposition of title in federally funded inventions at all, but rather only "regulate[s] the relationship between the government and its contractors, not third-party rights." Resp. Br. ("RB") 16; *see id.* at 15, 18, 19, 21, 40, 45. Roche asserts that the employee-inventor of a contractor remains the first owner of any funded invention, with the power to assign away ownership even before the invention exists. He is thus able to frustrate the statute's express objectives of giving the contractor title and protecting the Government's interests.

Second, to buttress its implausible argument, Roche tries to reframe the facts of the case. Based on the undisputed fact that Dr. Holodniy was allowed lab access and consultation with Cetus employees on

a part-time basis during a portion of 1989, Roche insinuates that the inventions embodied in the patents-in-suit were really the work of Cetus that Stanford has somehow spirited away. RB 5-11. But the facts as Roche spins them are very far from reality.

It is entirely clear that Dr. Holodniy, admittedly with assistance, is the one who developed the assay, Pet. App. 56a, and that the assay itself, while a useful tool, had no promise as a patentable invention. Thus, Cetus reviewers gave it their lowest rating on a five point scale for patentability, Pet. App. 38a, and approved its full disclosure by publication. On that basis, the work at Cetus was summarized in two abstracts and in a 1991 article published in the Journal of Infectious Diseases that "culminated" the work. JA 135; RB 8. After one year, these publications triggered the statutory bar to any conceivable claim of a patentable invention, 35 U.S.C. § 102(b), and any later patent necessarily depended on inventive work apart from what Dr. Holodniy did at Cetus. In fact, the later work at Stanford that gave rise to the patents used clinical testing of human patients taking antiretroviral drugs to "determine[] that HIV RNA, ... was a suitable 'marker' of drug efficacy," Pet App 5a, and also to define the actual critical levels indicative of drug efficacy.

The only co-inventors on any of the patents are Stanford employees, which Roche did not dispute for fifteen years prior to the filing of this case,[1] and

[1] Neither Cetus nor Roche asserted a claim of co-inventorship during the patent prosecution, in 2000 when Stanford

Roche cannot argue co-inventorship now. For this and other reasons, neither Roche's claim nor the decision below, Pet. App 15a, turn at all on whether the inventions were conceived during or after Dr. Holodniy's time visiting at Cetus.

Instead, Roche's claim rests wholly on Dr. Holodniy's purported assignment to Cetus in 1989, Pet. App. 4a, 14a-18a, and it is quite significant that federal funding was already in place at the time the assignment was made. Here, Roche again argues the facts, asserting repeatedly that Dr. Holodniy's work at Cetus was not aided by any Bayh-Dole grant. *See* RB 6-7 & n.1, 8, 12, 16, 21 n.8, 36, 44-45. But these unsupported assertions are plainly wrong, as is obvious from the JID article that Roche discusses at length. *Id.* at 8. Its opening footnote lists as grant support for that work the same NIH grants referenced on the patents, JA 135; Supp. JA 27, 50, 75, and the fact that these grants were in place by 1988 is readily confirmable from official governmental records. *See infra* at 22.[2]

(continued...)

approached Roche to negotiate a patent license, or any time prior to Stanford's suit in 2005—more than fifteen years after the Cetus work ended. *See* Opening Br. ("OB") 33; RB 11 n.4.

[2] Roche says that Stanford's opening brief asserts "for first time" that the work done by Dr. Holodniy at Cetus was federally funded. RB 6. That is because Roche has not before, in its BIO or otherwise, disputed that the inventions at issue were in fact federally funded, the oft-repeated claim and premise of this case. *E.g.*, Dkt. 111, at 8; Pet. 5. In any event, any claim that Dr. Holodniy's Cetus work was unfunded would be frivolous, given the record.

I. DR. HOLODNIY'S ASSIGNMENT TO CETUS WAS INEFFECTIVE BECAUSE BAYH-DOLE GIVES THE CONTRACTOR A CONDITIONAL RIGHT TO TAKE TITLE TO FEDERALLY FUNDED INVENTIONS THAT THE INVENTOR CANNOT TAKE AWAY

The text and structure of the Bayh-Dole Act, considered in light of its regulations and historical context, show that the statute comprehensively defines ownership rights in federally funded inventions. OB 30-38. Enacted against a backdrop of the Government taking title to most funded inventions, and a muddle of varying procedures, Bayh-Dole created a uniform hierarchy of rights and procedures. OB 9-12, 30-31, 35. Its first section states an intention to regulate "inventions made by nonprofit organizations," § 200, and its title and section headings evince an intent to govern the entire "[d]isposition of" "Patent Rights in Inventions Made with Federal Assistance." 35 U.S.C. ch. 18; § 202; OB 12.

The text of § 202(a) gives contractors a statutory right "to elect to retain title." OB 33-34. That legal right is subject to a governmental license and numerous procedural and substantive safeguards to protect the Government's interests. For example, if a contractor fails to timely disclose, elect to retain, or file a patent application on a subject invention, the Government may itself "receive title." 35 U.S.C. § 202(c)(1)-(3). And even if the contractor timely performs all of those requirements, the Government can still "march in" and force the contractor "to grant a ... license" to secure the public's interest. *Id.* § 203; OB 13-14.

Nothing in the statute references any need for the contractor to obtain an assignment from the inventor in order to trigger the Act. OB 34. Instead, Bayh-Dole takes a different path to recognizing "the equity of inventors" and defines their rights by entitling them to royalties and a subordinate possibility of receiving title. S. Rep. No. 96-480, at 33 (1979); 35 U.S.C. §§ 202(c)(7)(B), (d); OB 36-38. By defining the rights of contractors, the Government, and inventors, Bayh-Dole thus governs all rights in federally funded inventions.

A. Roche's Textual Argument Misreads The Words "Invention of the Contractor" and "Retain"

Roche's primary textual argument, that the statute applies only where the contractor already has received the inventor's interest by assignment, focuses myopically on a gross misreading of five words of the statute—the phrase "invention of the contractor" in the definition of "subject invention," § 201(e), and the word "retain" in § 202(a). RB 18-23.

1. Roche contends that there can be no "invention of the contractor," and thus no "subject invention" triggering the Act, unless the contractor already owns the invention by assignment from the inventor. RB 18-21. But this is not the natural understanding of the phrase, viewed in context, and the drafters could easily have said "any invention owned by the contractor" had they meant that.

More commonly, the word "of" is used to indicate origin. *See* Random House Dictionary of the English Language 999 (Deluxe Ed. 1985) (second definition in order of frequency: "to indicate derivation, origin, or source"); *accord* American Heritage Dictionary 862

(2d coll. ed. 1985) (most frequent definition).[3] Thus, a person describing the telephone as an "invention of Alexander Graham Bell" means that Bell invented the telephone, not that he owned the rights to it. The same meaning naturally follows when a noun is derived from the action that produced it—*e.g.*, "the writings of Emerson," or "the decision of the Court."

Because contractors are typically organizations and only individuals can be inventors, the phrase "invention of the contractor" is most reasonably construed to mean an invention made by the contractor through its employees. *See* OB 32. Roche argues that this cannot be, RB 20, but other language in the statute and regulations confirms that Congress intended precisely this meaning. The statute's preamble states that its policies and objectives apply to "*inventions made by nonprofit organizations* and small business firms." 35 U.S.C. § 200 (emphasis added). And the title of Bayh-Dole's implementing regulations defines their scope as addressing "RIGHTS TO INVENTIONS MADE BY NONPROFIT ORGANIZATIONS AND SMALL BUSINESS FIRMS UNDER GOVERNMENT GRANTS." 37 C.F.R. pt. 401 (Heading); *see also* 37 C.F.R. § 401.1(c) ("made by").

Since Bayh-Dole's statement of objectives and governing regulations expressly encompass inventions "made by" funded contractors, it would be

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[3] While the word "of" can sometimes indicate "a possessive relationship," that is a much less common usage. *See* Random House Dictionary of the English Language 999 (Deluxe Ed. 1985) (seventh definition). Roche's three cases that follow this usage, RB 18, therefore do not support its argument here.

odd if § 201(e)'s definition of "subject invention," establishing the Act's scope, did not also use the words "invention of the contractor" to reference one "made by the contractor" through its employees.

Finally, this interpretation of "invention of the contractor" is critical to protect third-party rights. Indeed, the insistence of Roche and its *amici*, BIO Br. 20-27; Intel Br. 18-22; PhRMA Br. 24-26, on their misconstruction of these words, while protesting the Act's supposed threat to third-party rights, is a bit like a child seeking mercy as an orphan after murdering his parents. By predicating a contractor's claim of Bayh-Dole title on the inventive contribution of its employees, this language leaves undisturbed the ownership rights derived from independent co-inventorship of unfunded third parties and their assignees. Certainly, also, it does not appropriate to a contractor inventions wholly conceived, and thus invented, by individuals unconnected to the funded university. *See infra* at 16-18.

Thus, far from rendering the phrase "invention of the contractor" superfluous, *see* BIO Br. 10-11; PhRMA Br. 7-8, Stanford's reading of the Act relies directly on that language as integral to a coherent and fair reading of the Act.

2. Consistent with its erroneous reading of "invention of the contractor," Roche contends that a contractor may "elect to retain" title only where the contractor already "owns" the invention by assignment. RB 22. While the word "retain" may sometimes carry that inference, its common definition, as "to *hold* or continue to hold *in possession*," Webster's Third New International Dictionary 1938 (1976) (emphases added); *see* RB 22

(definitions), does not require it. Given the prior history in which the Government had taken title to 80% of funded inventions, 126 Cong. Rec. 1993 (1980), describing the Act's conditional grant of title as allowing the contractor to "retain" it—rather than have the Government take it away—is quite understandable. OB 35. And that meaning of the word is compelled, because the Act viewed as a whole is plainly a comprehensive undertaking to define, as its title states, "Patent Rights In Inventions Made With Federal Assistance," 35 U.S.C. ch. 18, and not simply the bilateral rights of the contractor and the Government. OB 37, 39, 41.

A critical proof of this fact is that Roche's meaning of "retain" in § 202(a) cannot even be squared with its own usage of the term where it appears elsewhere in the Act. Under § 202(d), where "a contractor does not elect to retain title to a subject invention," the Government "may consider ... requests for retention of rights by the inventor." To explain away this provision's express addressing of inventor rights, Roche contends that § 202(d) applies only to "inventions [that] have already been assigned by the inventor to the contractor," RB 38-39, as it claims is necessary even to have a "subject inventon." Thus, Respondent claims that the contractor can only "retain title" to an invention that it already owns, while an inventor may be considered for "retention" of title only when he has assigned title away.

Since "identical words and phrases within the same statute should normally be given the same meaning," Roche's construction of the word "retain" must be rejected as irreconcilable with itself. *Powerex Corp. v. Reliant Energy Services, Inc.*, 551

U.S. 224, 232 (2007); *IBP, Inc. v. Alvarez*, 546 U.S. 21, 34 (2005).

Also, the Act's usage in other provisions of "acquire[] title" and "receive[] title," 35 U.S.C. §§ 203(a); 204, indicates that the statutory process by which the contractor "elect[s] to retain title," and fulfills the numerous other statutory requirements, does indeed result in it "acquir[ing] title." *See* OB 36. This conclusion is unmistakably confirmed by the legislative history. OB 38-42.

Roche's counterarguments are hypertechnical and unpersuasive. While the Act references other conceivable ways by which a contractor may get title *e.g.*, assignments from the Government derived from a federal-employee co-inventors, § 202(e)(2)—those situations are rare. The drafters plainly conceived of the detailed statutory process, including election to retain and compliance with numerous explicit statutory requirements, as the principal avenue by which the contractor would "acquire[] title under this subchapter," § 203(a). Indeed, if Roche were correct that a contractor's title must always flow from the inventor, the contractor would almost never "acquire title *under this subchapter*." This strange result also strongly suggests that Roche's reading is wrong.

B. The Purported "Absence of Vesting Language" Does Not Support Roche's Interpretation

In addition to misreading five words of the statute, Respondent's textual argument focuses on the supposed omission of appropriate vesting language. RB 23-26; *see* BIO Br. 14-15; Intel Br. 11-12; IPO Br. 15; PhRMA Br. 6-7.

First, this argument depends upon Respondent's misreadings of the words "invention of the contractor" and "retain." When those words are properly understood, the statute extends to federally funded inventions made by the contractor's employees, and creates a conditional right in the contractor to "hold" title to those inventions by complying with the statute's many requirements. *See supra* at 5-9.

Second, this argument simply ignores the statute's comprehensive character in defining the rights of all parties, and setting numerous conditions upon the contractor's continued right to title, on whose failure "title" may revert to the Government or, at times, to the inventor. OB 12-16, 30-38. The statute defines these requirements and consequences with great care, and its language leaves no doubt that what is at stake is "title" to the invention. *E.g.*, §§ 202(c)(1)-(3),(d).

It is quite implausible that the statute, while setting forth this comprehensive scheme in painstaking detail, omitted to mention anywhere what Roche argues is the key triggering event – an assignment from the inventor. This is especially true given the federal interest at issue. *See infra* Section I.D. Notwithstanding the United States' substantial stake in advancing its statutory interests, resting on billions of dollars in research funding, Roche would render the Act inapplicable and the federal interest largely unprotected whenever the contractor fails to get an assignment with priority over even the broadest imaginable assignment to a third-party – like the one Cetus extracted here.

In a similar vein, Roche notes that the legislative history does not contain statements affirmatively

denying that the contractor would be required to secure an assignment from its employee-inventor. RB 41. No such statements should be expected where the new statute supplanted many agency vesting statutes by which the Government had simply taken title without regard to any other assignments. Indeed, Roche's argument is an unsupportable reversal of the principle of *expressio unius est exclusio alterius*. OB 34. The failure to discuss any need for an assignment when so many other requirements were being specifically imposed strongly indicates that no such requirement exists.

C. Roche's Reading Of 37 C.F.R. § 401.14(a), ¶ (f)(2) As Requiring Employee Agreements To Assign Inventions To The Contractor Is Plainly Wrong

Roche also purports to find a requirement that contractors secure assignments of title from their inventors in vague language from the standard patent rights clause, 37 C.F.R. § 401.14(a). RB 42. That language is found in ¶ (f)(2), which requires the contractor to demand a written agreement from its technical employees:

> to disclose promptly in writing ... each subject invention made under the contract in order that the contractor can comply with the disclosure provisions of [37 C.F.R. § 401.14(a), ¶ (c)], and to execute all papers necessary to file patent applications on subject inventions and *to establish the government's rights in the subject inventions*.

37 C.F.R. § 401.14(a), ¶ (f)(2) (emphasis added).

Roche suggests, and its *amici* directly assert, an analogy between the last clause of this provision, requiring that employees agree to "execute all papers necessary ... to establish the Government's rights in subject inventions," and the form agreement under the pre-Bayh-Dole IPA clauses, through which contractor employees were required "promptly [to] report and assign all subject inventions." RB 42; *see* AAUP Br. 10-11; BIO Br. 16-17; Intel Br. 6-7, 16-17; IPO Br. 17 n.10; PhRMA Br. 10-11.

This is wrong for several reasons. First, by its terms, ¶ (f)(2) only applies where a "subject invention" already exists. Thus it cannot possibly be the source of a duty on inventors to make assignments to contractors, without which Roche says there is no "subject invention" triggering the Act.

Second, whereas the IPA agreements expressly mandated non-clerical workers to "assign all subject inventions," *see* RB 42, ¶ (f)(2) omits that language, and instead refers to executing papers necessary to "establish the government's rights in the subject inventions." The decision to omit previous agreement language that expressly required an assignment is hardly an indication the drafters intended to maintain that requirement. *Brewster v. Gage*, 280 U.S. 327, 337 (1930).

Third, Roche's divined meaning is especially odd given that, elsewhere, when 37 C.F.R. § 401.14 requires conveyance of title, it is unmistakably clear—as one would expect. *See, e.g.*, 37 C.F.R. § 401.14(a), ¶ (d) ("The contractor will convey ... title to any subject inventions"); ¶ (f)(1)(ii). Likewise, it refers to the "inventor" when the inventor is at issue. *See, e.g., id.* § 401.14(a) ¶¶ (c)(1); (k)(2); (k)(3),

(7)(2)(B). Vague language buried in a regulation would be a strange way to require an assignment of title, unmentioned in the statute and without which the Act is supposedly rendered wholly inapplicable.

Finally, ¶ (f)(2) should be read in context with the statutory provisions it is designed to implement, not by reference to prior regulations that the Act superseded. So viewed, ¶ (f)(2)'s requirements plainly refer to rights and duties actually set out in § 202(c). Paragraph (f)(2)'s first clause, requiring that employees agree in writing to "disclose promptly" the making of any subject invention, plainly supports the contractor's own disclosure duty in § 202(c)(1). Likewise, the next clause, demanding that employees agree "to execute all papers necessary to file patent applications," is in direct service of § 202(c)(3)'s requirement that the contractor do just that.

The clause at issue, demanding a further agreement to "execute papers necessary ... to establish the Government's rights in the subject inventions," similarly finds direct antecedent in the very next provisions of the statute, §§ 202(c)(4), (6). Those sections assure the Government a fully paid up license and related rights, and require that the patent specification include a statement of the Government's support and rights. The final phrase of ¶ (f)(2) references documents necessary to secure these rights, and perhaps other incidental documents. *See* United States Patent and Trademark Office, Forms, http://www.uspto.gov/forms/index.jsps.

In short, ¶ (f)(2), whose application is only triggered by the existence of a subject invention, certainly is not the source of any legal requirement that contractors secure assignments of title, as Roche

says is necessary before there can be a subject invention in the first place.

D. Roche's Construction Directly Undermines The Statute's Express Objective To Protect The Interests Of The Government

Roche and its *amici* have no answer to the fact that their reading critically undermines Bayh-Dole's major objective of "ensur[ing] that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions." 35 U.S.C. § 200; *see* OB 48-51; U.S. Br. 31-33; CVSG Br. 18.

The statute seeks to protect these interests by allowing the Government to initially take title based on enumerated special circumstances, § 202(a)(i)-(iv); to later "receive title" in other instances, § 202(c)(1)-(3), and also to "march-in" and confer rights upon another, § 203. The Government is thereby enabled to enforce an array of statutory and contractual duties to be carried out by the contractor, including, among others, the use of royalties only for education and research, § 202(c)(7)(C), and honoring the preference for United States manufacture, § 204. If a funded inventor working for a contractor had the power to independently assign an ownership interest in the invention to a third party, these avenues of Government recourse to enforce its interests would be gravely undermined.

Indeed, Roche's only suggested solution where an inventor has transferred title to a third party is "for the Government to sue [the contractor] for breach of contract, including, if appropriate, reclaiming the amount funded." RB 54. But how is there even a

breach of contract if there is no "subject invention"? *See supra* at 12. In any event, this cumbersome, inefficient, and, here, likely time-barred remedy, is certainly not one of the specific Government remedies carefully set out in the Act.

E. Roche's Arguments Raising The Specter Of Due Process Violations, Takings From Third Parties, And Diminished Collaboration, Rest On A Strawman Reading Of The Act That No Party Endorses

Respondent and its *amici* devote significant briefing to unsubstantiated assertions that bad things will happen if the Act is read as its fair meaning in context would indicate. Upon examination, these assertions have no basis under the construction of the Act that Stanford and the United States urge the Court to adopt. Even if they did, these policy arguments are more appropriately addressed to Congress, not this Court.

Respondent argues that the statute cannot affect the rights of third parties because it contains no procedural protections of their rights, RB 28-31, and that Stanford's reading of the statute would work an unconstitutional taking of property from third parties and a denial of due process, RB 43-46. It further argues, largely based on these concerns, that reading the statute as Stanford does will substantially "chill innovative collaboration." RB 50-52. Roche's *amici* join the chorus trumpeting this parade of horribles. BIO Br. 26; Intel Br. 18-22.

1. The statute expressly defines the rights of a funded contractor's employee-inventors, and there can be no serious contention that this prospective definition constitutes a substantive violation of rights

Given that the inventor's possibility of securing title under the clearly defined statutory scheme is remote and entirely within the Government's discretion, § 202(d), the absence of an explicit statutory legal remedy to secure it is hardly surprising.

2. As to unrelated third parties whose rights Roche and its *amici* insist will be imperiled by Stanford's reading of the Act, the statute provides no procedural protections for those parties because it does not deprive them of any rights.

For example, Roche and its *amici* contend that Stanford's reading would take away vested rights of third parties—*e.g.*, private businesses—who are assignees of independent co-inventors who did not work for the contractor or utilize federal funding. RB 43-46; IPO Br. 18-21; PhRMA Br. 25. But, as Stanford's *amici* AAU noted, if Cetus employees had been co-inventors of the patents-in-suit, the Act would not govern disposition of the Cetus co-inventors' interest in the inventions. AAU Br. 23-24. This issue has no bearing on the outcome here, since there were indisputably no Cetus co-inventors, but Stanford entirely agrees with AAU, whose brief speaks for scores of universities. A funded contractor's ownership interest under Bayh-Dole is limited to the interest arising from the inventive activities of its own funded employees. Thus the Act does not give a federal contractor a title that overrides that of independent, unfunded co-inventors—who may often work for private companies. The plain-meaning interpretation

Stanford advances thus fully protects independent co-inventors.[4]

This conclusion rests on the statute's text. Just as an "invention of the contractor" is one made by the contractor's employees, *supra* at 5-7, an invention co-invented by employees of a private company working without federal funding is also an invention of that inventor and that company. Thus, an invention may be both "of the contractor" and "of" another who is independently responsible for co-inventing it, in which event the contractor's rights derived under the statute must co-exist with the co-inventor's right to an equal and undivided interest in the invention.

This reading of the statute is required by the language of § 202(e), which recognizes that where Government employees are co-inventors with a funded contractor's employees, the federal agency may, "for the purpose of consolidating rights in the invention," assign to the contractor the title it receives from its own employee. By providing for this eventuality, this section shows that the contractor does not otherwise get title under the Act to the interest arising from the federal employees' co-inventorship. No reason appears why co-inventors in private industry should not be treated by the Act in the same way that it expressly deals with Government co-inventors.

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[4] Roche's assertion that this conclusion is "irreconcilable with Stanford's argument" is baffling. RB 36. Stanford was able to perfect its title and to secure complete ownership of the patents-in-suit only because all co-inventors were Stanford employees.

Thus, Respondent's proposed lodgings, reflecting that Stanford itself "shares ownership with other private entities of numerous patents" to which Bayh-Dole applies, are unsurprising. RB 35 & n.13. That result follows directly where privately funded individuals associated with corporations are co-inventors of the inventions, making the corporation a co-owner with Stanford.

3. Roche's *amici* raise a similar alarm that Bayh-Dole may be a means of appropriating inventions originally conceived without Government funding by private researchers, and later reduced to practice by a funded contractor. BIO Br. 7, 21-22; Intel Br. 19-20. But as Stanford noted, OB 32 n.11, a contractor's employees are only co-inventors if they play a part in conception, and a privately conceived invention does not become the property of a university when the university's employees later reduce the invention to practice with the aid of federal funding. While the disjunctive language of § 201(e)—requiring that the invention be "conceived or first actually reduced to practice" in the course of funded work—may be satisfied, there is no "invention of the contractor" if no employee plays a part in conception.[5]

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[5] In a misdirected tangent, Roche suggests that the district court erred in finding sufficient proof that the inventions were produced "in the performance of work under a funding agreement." *See* RB 30-31. But the Federal Circuit did not address that issue, and it is not before this Court. Roche presses this issue on the erroneous premise that Stanford's reading of the Act allows a federal contractor to elect title and "divest third parties of intellectual property rights." RB 31. Because Roche never had any rights to the inventions, it is not

4. For these reasons, Roche and its *amici* offer no basis for asserting that Stanford's reading of the Act will somehow impair collaboration between universities and non-funded private companies.

First, increased certainty of the contractor's title to federally funded inventions will make potential licensees more willing to purchase an exclusive or other license. *See* NVCA Br. 7; BIO Br. 20. Roche's interpretation of the Act creates uncertainty because it permits enforcement (sometimes years later) of an undisclosed assignment of future rights in ongoing federally funded research. Indeed, Roche and some *amici* acknowledge this effect, but dismiss it by noting that "such risks are not unique to federal contractors," RB 47, and that such uncertainty "is not the end of the world," AIPLA Br. 30-31.[6]

Second, greater certainty of the contractor's title will also make it easier, not harder, for universities and industry to enter into reliable collaboration agreements to facilitate inventive research. Certainty of the contractor's title makes it possible for industry collaborators to contract only with the contractor, and not also with all individual

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(continued...)

being "divested" of any rights by Stanford's election of title, whatever level of proof is required.

[6] It is no answer to require warranties. *See* PhRMA Br. 18-22. The greater the uncertainty of title, the less likely universities will be to enter into technology transfer agreements warranting clear title. Also, such warranties may be a poor substitute for certainty in the eyes of a technology company seeking a sound license, not a warranty-enforcing lawsuit.

researchers. Such university-industry arrangements commonly contemplate that the collaborating private company will have a right at some price to an exclusive or other license—as the NIH interpretive guidance envisions, OB 54, and as was actually negotiated in this case. AAU Br. 25. Thus, increased certainty that the university actually will have clear title and the ability to deliver such a license can only make such arrangements more reliable, thus giving a sounder basis for collaboration "between commercial concerns and non-profit organizations." 35 U.S.C. § 200.

II. EVEN ASSUMING CONTRACTORS MUST SECURE AN ASSIGNMENT, STANFORD GOT TWO SUCH ASSIGNMENTS, AND THE ACT MUST AT LEAST BAR FUNDED EMPLOYEE-INVENTORS FROM ASSIGNING AWAY THE UNIVERSITY'S PROSPECTIVE BAYH-DOLE RIGHTS

For the reasons set forth above, the Bayh-Dole Act creates a conditional right of funded contractors to take title to the inventions made by their employees with the aid of federal funding that does not depend upon the contractor first securing an assignment. This Court's recognition of that fact is of great importance because the uncertainties caused by a contrary ruling would severely impair achievement of the Act's objectives.[7]

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[7] In addition to the critical uncertainty about the reliability of the contractor's title to the funded inventions, requiring an assignment would raise a new layer of interpretive questions. Does the Act create a legal obligation on funded contractors to secure inventor assignments to funded inventions? *E.g.*,

However, even a ruling that contractors must get an assignment of title in order to trigger the Act would not justify affirming the decision below. For Stanford secured an assignment of future rights—*twice*—which Dr. Holodniy executed in 1988 and 1995. Pet. App. 41a, 94a, 112a. With such an assignment in place, the Bayh-Dole Act would mean very little indeed if it did not bar the employee-inventor working under federal funding from making a later effective assignment of the same rights to an independent third party, thus substantially impairing the statutory interests of both the Government and the contractor.

This conclusion is most emphatically clear on the facts of this case, where the two federal grants on which Stanford's Bayh-Dole title depends were in place during 1989, and supported Dr. Holodniy's research at Cetus. The JID article—which Cetus approved for publication, JA 38, and which Roche concedes represented the "culminat[ion]" of Dr. Holodniy's Cetus visits, RB 8—expressly identifies the two grants as support for the published research: AI-27666 for AIDS-related clinical trials,

(continued...)

PhRMA Br. 10-11. If so, does it also require such inventors to make such assignments, and what happens if they fail to do so? *See, e.g., Heinemann v. United States*, 796 F.2d 451, 452, 456 (Fed Cir. 1986) (Government still has title despite its own employee's failure to make a required assignment); AAU Br. 7-9. Perhaps most importantly, how can the Government secure sufficient rights to protect and enforce its statutory interests? *See supra* Section I.D; Pet. App. 19a.

and AI-27762 for establishing a Center for Aids Research. JA 135, 98-99.

Ignoring the JID article, Roche now baldly and repeatedly denies that Dr. Holodniy's research while he visited at Cetus was federally funded. RB 6-7, 8, 12, 13, 15 n.7, 16, 21 n.8, 36, 44-45. It does so without citing any evidence, and relying only on out-of-context quotations from Stanford's Federal Circuit briefing. RB 6-7 & n.1. But these quotations are from arguments addressing the point at which the critical inventive work began at Stanford, not the point at which federal funding began, and Roche's attempted inference is simply not credible. Moreover, what is explicit in the JID article is confirmed by the public record. NIH, Project Report, Project Numbers 27666, 27762, http://bit.ly/Redirect-To-NIH-Website-With-Grant-27666-History, http://bit.ly/Redirect-To-NIH-Website-With-Grant-27762-History (NIH sites showing grants began in 1988); *see also* JA 28, 96, 98. Both courts below held that Dr. Holodniy visited Cetus to advance his research at Stanford, Pet. App. 18a, 63a-64a, so these grants applied to his activities there.

Thus, Dr. Holodniy's research at Cetus was conducted when Stanford had equitable rights in the fruits of his research based on the 1988 agreement to assign, and also had an expectation of receiving future title under the Bayh-Dole Act because the work was already federally funded. Accordingly, even assuming that the Act depends on an assignment from the inventor to trigger its application, the Act must at least mean that its policies may not be directly frustrated by a further assignment of rights to a third party. Such an

assignment is in derogation of both the prior assignment of rights to Stanford and the express policies of the Act.

The conclusion that Dr. Holodniy's purported assignment to Cetus should have no legal effect is buttressed by equity's substantial role in the determination of patent rights, especially regarding rights in inventions that do not presently exist. OB 59-60. As *amicus* Shukh explains, both the Cetus assignment and Dr. Holodniy's earlier agreement to assign Stanford rights in future inventions transferred equitable but not legal title to the yet-to-be-created inventions.[8] In evaluating the equities to determine which ownership claim should be recognized, the Act's express objective to direct title to the funded contractor must be given paramount significance.

Other equities also weigh heavily in favor of Stanford and against giving legal effect to the Cetus assignment. One, of course, is Stanford's first-in-time receipt of an equitable interest. Another is that

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[8] *Amicus* Shukh's brief shows that this Court has never approved of the Federal Circuit's case law holding that equitable title can automatically convert into legal title, Pet. App. 13a; *see Filmtec Corp. v. Allied-Signal Inc.*, 939 F.2d 1568, 1572 (Fed. Cir. 1991), and that holding is contrary to longstanding authority. *See* Shukh Br. 18-24. Indeed, the statutory authority for assignment of patent rights permits assignment "in law" of only present interests, *i.e.*, "patents" or "applications." 35 U.S.C. § 261. Any future interest, such as Cetus supposedly received, can be assigned, if at all, only in equity. *Mitchell v. Winslow*, 17 F. Cas. 527, 531 (C.C.D. Me. 1843) (Story, J.) (A present assignment of future rights "may be enforced as such a [present] contract in rem, in equity.").

neither Cetus nor Roche asserted its alleged rights for more than fifteen years, and then only as a defense to litigation after the time to pursue an affirmative ownership claim had lapsed.

Not only has Roche's delay undone certainty and rendered relevant evidence unavailable, *e.g.*, Dkt. 95-4, at 246:16-248:23; *cf.* JA 43, but it also has no justifiable basis. Roche's attempted explanation is a non sequitur. The fact that Roche "commercialized PCR-based testing kits," RB 57, in no way preserved its alleged ownership rights under the assignment or counters the injustice and disruption resulting if Roche could assert title now.

In short, even if the Act required contractors to secure inventor assignments of title, Stanford did that, and Dr. Holodniy's purported assignment to Cetus would still be ineffective to convey title to the patents-in-suit to Roche.

CONCLUSION

The decision below should be reversed.

Respectfully submitted,

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SUPPLEMENTAL BRIEF

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IN THE

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ROCHE MOLECULAR SYSTEMS, INC., *et al.*,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

SUPPLEMENTAL BRIEF FOR RESPONDENTS IN RESPONSE TO BRIEF OF THE UNITED STATES

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CORPORATE DISCLOSURE STATEMENT

The Rule 29.6 statement included in Respondents' brief in opposition remains accurate.

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SUPPLEMENTAL BRIEF FOR RESPONDENTS IN RESPONSE TO BRIEF OF THE UNITED STATES

Respondents respectfully submit this response to the government's brief filed at the Court's invitation ("Inv. Br.").

SUMMARY

1. The government offers a reformulated Question Presented untethered to the facts, which the government seeks to dismiss as "fortuit[ies]." Inv. Br. 15, 21. The actual facts cannot be brushed aside. Dr. Mark Holodniy was not a rogue inventor who secretly "defeated" Stanford's rights. Inv. Br. I. Ra-

ther, as the district court found, Holodniy went to Cetus at Stanford's direction, and Stanford had actual and imputed notice of his assignment. Pet. App. 16a-17a, 64a. The invention was conceived before Holodniy left Cetus. *Id.* 14a, 56a-58a. This chronology, as well as the agreements' terms, necessarily informed and limited the Federal Circuit's ruling, and the court made clear that the government's rights were not at issue. Pet. App. 20a n.1. There is no reason for this Court to review a limited decision on an unusual factual record in search of an issue that is not presented here and may never be presented at all. Indeed, the government cannot identify *even one* other case that the ruling below would affect.

2. The government's proposed resolution of the question it urges on the Court is both unsupported by the Bayh-Dole Act and misguided as a matter of policy. The statute does not allow a contractor to "obtain" title (Inv. Br. 17), nor does it create a "presumption" of contractor ownership (*id.* 16-17)—a notion the government derives not from the Act's text, but from a committee report that considered a materially different House bill. The Bayh-Dole Act governs funding agreements between the government and federally-funded research institutions; it does not confiscate intellectual property rights from non-funded entities whose private resources and expertise lead to the conception of inventions. The government's rule would chill collaboration between universities and private research firms; indeed, it would put privately-funded firms in a *worse* position than entities who take federal funds.

ARGUMENT

I. THE DECISION BELOW DOES NOT WARRANT REVIEW

The government replaces Stanford's Question Presented with yet another one the Federal Circuit did not decide. The government's reformulation—"Whether an inventor who is employed by a contractor that elects to retain rights in an invention ***may defeat*** the contractor's right to retain title under the Bayh-Dole Act" (Inv. Br. I (emphasis added))—ignores critical facts that circumscribe the effect of the decision below.

The government's assertion that "[t]he patented process was developed by researchers at [Stanford] using federal funds" (Inv. Br. 7) is wrong. The invention was conceived and the assay completed at Cetus *before* Stanford performed any work using federal funds. *Id.* 14a, 56a-58a. Stanford offered no alternative conception date. *Id.* 58a n.7.

Before any involvement of federal funding in the research, Stanford itself (through Thomas Merigan) directed Holodniy to "spend time at Cetus to develop a better assay." *Id.* 4a, 35a, 64a, 69a. Holodniy arrived at Cetus "with the specific intent" and "goal" of developing such an assay. *Id.* 56a, 64a. Holodniy executed the assignment "in the course of Stanford's business," and Stanford had actual and imputed notice of it. *Id.* 16a-17a, 64a. Accordingly, the invention was conceived and the assay completed while Holodniy "was assigned a lab bench in Cetus' Clinical Group, and had access to Cetus personnel, materials, and equipment." *Id.* 35a. Holodniy spent approximately nine months "receiving technical infor-

mation from Cetus scientists and proprietary physical materials from Cetus," all of which were the fruits of private investment, not Bayh-Dole funds. *Id.* 36a.[1]

This is not a case, as the government suggests, of an inventor's "wishes" overriding the Bayh-Dole Act. Inv. Br. 11. Instead, the inventor acted with notice to the contractor. Pet. App. 16a-17a, 64a. And the Federal Circuit clearly linked its ruling to the facts of this case, particularly the nature and timing of Holodniy's agreements. *E.g.*, *id.* 12a (discussing Stanford's use of a future assignment, rather than present assignment); *id.* 16a (Stanford had "at least" constructive notice of Holodniy's agreement with Cetus); *id.* 19a (relying on the fact that Holodniy's assignment to Cetus predated Stanford's election to retain title by six years); *id.* (finding no authority suggesting that Stanford could use the Act to void "any *prior*, otherwise valid assignments" (emphasis added)); *id.* 20a ("*prior* contractual assignments" (emphasis added)); *id.* 21a (similar).

The Federal Circuit did not decree a broad rule governing all federal funding cases, and it did not address the alternative fact patterns that the government imagines. Inv. Br. 17 (hypothesizing situation in which "the terms or even existence of [an assignment are] unknown to the contractor"). Indeed, the court left open the possibility that Stanford or

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[1] Holodniy's salary was paid by a National Research Service Award. Decl. of Thomas C. Merigan ¶13 (Dkt. 112, Nov. 15, 2006). Such awards are not subject to the Bayh-Dole Act. *See* 35 U.S.C. 212.

the government might have "some other legal recourse to recover Holodniy's rights" in this very case. Pet. App. 20a n.1.

Accordingly, as Respondents explained (Opp. 11-17), certiorari is inadvisable for at least four reasons: (1) the question Stanford presented for review is far broader than the question actually decided; (2) the government's rights are the same regardless of the outcome of this petition; (3) a reversal in this case may well ultimately have no effect on the outcome, due to the judgment that the patents are invalid; and (4) the peculiar facts that implicated the Bayh-Dole Act are not known to have arisen in any other case.

The government does not meaningfully contest these facts. First, the government acknowledges that the question in Stanford's petition—whether Stanford's rights could be "terminated unilaterally by an individual inventor" (Pet. i)—is not presented. Inv. Br. 21 (Stanford "has not been deprived of all rights in the inventions because it obtained valid assignments from Holodniy's co-inventors"). Second, the government admits that its own rights—an irrevocable paid-up license—are exactly the same under the Federal Circuit's judgment as they would be were this Court to reverse. *Id.* Third, the government acknowledges that, because the district court held the patents invalid as obvious, a reversal by this Court may have no effect on the outcome. *Id.*

The government attempts to dismiss these serious vehicle problems as a "fortuity" (Inv. Br. 15, 21), even though *every* vehicle problem is in some sense a "fortuity" that happens to arise in one case but might not in another. *E.g.*, *Kenyeres* v. *Ashcroft*,

538 U.S. 1301, 1305-06 (2003) (Kennedy, J., in chambers) (certiorari was not "appropriate" given the particular facts of the case, even though the issue was "significant" and produced an "acknowledged disagreement among the lower courts"). Here, the "ameliorating circumstances" (Inv. Br. 21) limit any harm to Stanford and eliminate any harm to the government, thereby further disfavoring review.

Regarding the fourth reason for denying review—the apparently unprecedented factual scenario—the government says only that federal funding under the Bayh-Dole Act is widespread. Inv. Br. 1, 16. But the *statute's* general importance says nothing about the specific importance of the *Question Presented*. The government, Stanford, and Stanford's amici have not identified a single other case that would even arguably be affected by the Federal Circuit's ruling.[2]

For the decision below to apply as "binding precedent" (Inv. Br. 21), the following factual predicates would have to exist:

> 1. a university requires a researcher to execute an "agreement to assign" intellectual property, not a present assignment (Pet. App. 13a);

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[2] Unlike the petitioner in *Fidelity Federal Bank & Trust* v. *Kehoe*, 547 U.S. 1051 (2006), neither Stanford nor the government faces any liability here, much less "$40 billion." *Id.* (Scalia, J., concurring in denial of certiorari).

2. the university sends the researcher to collaborate with a private entity that receives no federal funds (*see supra* pp. 3-4);

3. the researcher signs a *present* assignment of intellectual property to the private entity as a condition of access to that entity's expertise and materials (Pet. App. 35a-36a);

4. the university has notice of the researcher's assignment under state law (*id.* 17a, 64a);

5. the researcher conceives of an invention while working at the private entity without using federal funds (*id.* 35a-36a; *supra* pp. 3-4);

6. the researcher returns to the university, which then uses the already-conceived invention in further work done subject to federal funding (Pet. App. 5a, 39a);[3]

7. the university obtains a patent covering the invention that was previously conceived at and assigned to the private entity (*id.* 3a-4a, 41a);

8. the private entity practices the invention (*id.* 5a); and

9. the university chooses to sue the private entity for infringement rather than cooperate

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[3] Stanford has never disclosed the terms of the federal grant that supposedly funded Stanford's work after Holodniy returned from Cetus. Opp. 6.

to commercialize the invention for the public good.

If anything in this case is a "fortuity," it is this chain of highly unusual and improbable facts. The government offers no reason to conclude that they have ever recurred or ever will. Universities can avoid the first factual predicate above by using present assignments, as many already do. Opp. 15. The government ventures that a "massive number of past and present agreements" exist between universities and researchers (Inv. Br. 20), but it does not suggest that many employ future assignment clauses or that *any* have produced events similar to those in this case.[4]

Unable to present this case as anything other than atypical, the government seeks to portray the Federal Circuit's decision as "not dependent on the particular facts of this case." Inv. Br. 19. But even if the government were right about the breadth of the court's ruling—and it is not—the government still identifies no case, past or present, where the Federal Circuit's ruling (even as misconstrued by the government) would affect the outcome. If the government is right, there will be other opportunities for this Court to address its reformulated question on an

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[4] Notably, state-law remedies for rescinding an assignment might be available if a "rogue inventor" were ever to execute a secret assignment without his employer's knowledge (*see* Inv. Br. 17). *E.g.*, *Larson* v. *Correct Craft, Inc.*, 569 F.3d 1319, 1326-27 (Fed. Cir. 2009) (remanding claims for rescission of patent assignments); *Heidelberg Harris, Inc.* v. *Loebach*, 145 F.3d 1454, 1457 (Fed. Cir. 1998) (patent assignment rescinded).

appropriate record. As the government admits, questions regarding the interplay of the Bayh-Dole Act and contract law may arise "in any type of property dispute" and, in fact, have arisen in circuits other than the Federal Circuit. Inv. Br. 20; *see* Opp. 14 (citing cases). The Federal Circuit's denial of rehearing en banc in *this* case does not suggest that "further percolation" is unlikely. Inv. Br. 20. The more plausible conclusion is that the en banc court, like the panel (Pet. App. 20a n.1), correctly viewed the panel's ruling as limited to its facts and unlikely to govern many (or perhaps any) future cases.

The Court should reject the government's contention that the Federal Circuit misunderstood the scope of its own decision. The panel did not purport to decide a "pure question of law" divorced from the peculiar record in this case. Inv. Br. 19. The government's concern about how the Federal Circuit *might* decide future cases on different facts is not a reason for this Court to review an issue that apparently has not arisen before and may never arise again; the government's issue "can await a day when the issue is posed less abstractly." *The Monrosa* v. *Carbon Black Export, Inc.*, 359 U.S. 180, 184 (1959) (dismissing writ); *see also Caldwell* v. *Quarterman*, 549 U.S. 970 (2006) (statement of Stevens, J.) (denial of certiorari is appropriate where the court of appeals' "narrow holding is unlikely to produce injustice"); *Conway* v. *California Adult Auth.*, 396 U.S. 107, 110 (1969) (declining to adjudicate "the purely artificial and hypothetical issue tendered by the petition for certiorari").

II. The Government's Position Has No Support In The Statute Or Legislative History And Would Chill Innovative Collaboration

The government's position rests on two fundamental errors. First, the government misstates the statute, contending that it allows a federal contractor to "*obtain*" title, a word the Act does not use. Inv. Br. 17 (emphasis added). The Act provides only that a contractor may elect to "retain" title (35 U.S.C. 202(a)), a word that presumes that the contractor already has title to the invention, whether the contractor is an individual inventor who received title automatically or an organization that received a valid assignment from the inventor under 35 U.S.C. 261.

The government's second error is its belief that the Bayh-Dole Act created a "presumption" that a federal contractor automatically receives title to an invention developed using federal funds—a proposition the government bases not on the Act, but on a single sentence in a report of the House Committee on the Judiciary. H.R. Rep. No. 1307, 96th Cong., 2d Sess. Pt. 1 at 5 (1980) (House Report) (quoted at Inv. Br. 12, 16-17). But that report considered not the Act's final text, but an earlier version providing that a contractor "*will acquire title* to its contract invention" if certain prerequisites were met. *Id.* at 43 (quoting H.R. 6933, 96th Cong., 2d Sess. §383(a)) (emphasis added).

By contrast, a Senate report commenting on the language that was eventually enacted confirmed that a contractor's election permitted it to keep the rights *it otherwise possessed*: contractors "are to have the

right to elect to retain worldwide ownership *of their inventions*." S. Rep. No. 96-480, 96th Cong., 1st Sess. 31 (1979) (Senate Report) (emphasis added)); *see also id.* at 32 (failure to comply with reporting requirements could result in a contractor losing "*its rights* to an invention" (emphasis added)). Section 202(a), as enacted, simply does not govern a situation like this one, where a contractor does not possess all rights to an invention, but rather *shares* them with a private firm like Cetus that made major contributions to and enabled the invention without the benefit of receiving federal funds.[5]

Nothing in the legislative history the government cites suggests that Congress intended to supplant ordinary assignments that are valid under applicable law. *See Fenn* v. *Yale Univ.*, 393 F. Supp. 2d 133, 141-42 (D. Conn. 2004) (the Act regulates "relationships of small business and nonprofit grantees with the Government, not between grantees and the inventors who work for them"). Rather, Congress was concerned with allocating rights between contractors and *the government*. *See* House Report at 2 (bill evolved from "recommendations on government pa-

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[5] Section 202(d) gives agencies "the authority to leave rights with individual inventors in cases when contractors do not elect rights." Senate Report at 33. It has no application in situations where the contractor elects to retain the rights it otherwise obtained—here, Stanford's rights through assignments by Drs. Merigan and Katzenstein—but has not obtained, and therefore cannot "retain," the rights of a private entity whose contributions to the invention were not federally funded.

tent policy"). The Federal Circuit's ruling did not disturb that allocation.[6]

The government's reliance on 35 U.S.C. 210(a) is also misdirected. Inv. Br. 16. Section 210(a) provides that the Bayh-Dole Act "take[s] precedence" over other laws that would dispose of rights "in a manner that is inconsistent with this chapter" and then specifically lists 21 laws identifying agency patent policies. The canons of *ejusdem generis* and *expressio unius est exclusio alterius*, as well as the legislative history, confirm the limited effect of Section 210(a): to "take precedence over a number of statutory provisions that currently control to varying degrees *the patent policies of some agencies*." Senate Report at 35 (emphasis added). Section 210(a) never mentions the Patent Act's section governing assignments (35 U.S.C. 261)—a telling omission, given that the Bayh-Dole Act amended the Patent Act.

Finally, the policies underlying the Bayh-Dole Act are served by the status quo in this case, not by the government's position. Respondents commercialize HIV test kits built in Branchburg, New Jersey and distributed from Indianapolis, thereby creating American jobs and furthering American public health. 35 U.S.C. 200, 204. Stanford "retain[s]" full title from the co-inventors and rights to commercial-

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[6] *Platzer* v. *Sloan-Kettering Inst.*, 787 F. Supp. 360 (S.D.N.Y. 1992) (cited at Inv. Br. 13) ruled only that the Bayh-Dole Act did not imply a private right of action for inventors. *See id.* at 364-65. That conclusion supports the Federal Circuit's ruling that the Act does not regulate Holodniy's assignment.

ize the inventions. *Id.* 202(a). And the government retains its "march-in" rights to compel licensing as appropriate. *Id.* 203.

The Bayh-Dole Act envisions forfeiture of intellectual property only in rare situations where a contractor that has taken federal funds later *breaches* its obligations. 35 U.S.C. 202(c)(1)-(2); *Campbell Plastics Eng'g & Mfg., Inc.* v. *Brownlee*, 389 F.3d 1243, 1249 (Fed. Cir. 2004) (upholding forfeiture where contractor breached its contract by failing to disclose the invention). Nothing in the Act suggests that Congress meant to visit that punishment on an innocent company like Cetus that did not even assume obligations to the government, let alone breach them. The government's suggestion that Cetus has no right to use an invention conceived using Cetus's own resources puts Cetus in a worse place than it would have occupied had it actually *received* federal funds. The Act cannot be read to produce such an arbitrary result.

The government's contentions would chill the very "collaboration between commercial concerns and nonprofit organizations, including universities" that the Bayh-Dole Act sought to foster. 35 U.S.C. 200. The government does not suggest how, under its rule, a small firm like Cetus could protect its intellectual property while collaborating with a university. The government, like Stanford, appears to believe that discoveries conceived on the back of private investment may be snatched away retroactively if a university subsequently—and without notice to or consent from the private entity—decides to incorporate them into federally-funded projects. *See* Pet. 12. Such a rule would discourage scientific coopera-

tion with no countervailing public benefit, only a windfall for Stanford.

CONCLUSION

The petition for a writ of certiorari should be denied.

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AMICUS CURIAE BRIEF

19

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In the Supreme Court of the United States

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, PETITIONER

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING PETITIONER

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QUESTION PRESENTED

The University and Small Business Patent Procedures Act of 1980, 35 U.S.C. 200 *et seq.*, commonly known as the Bayh-Dole Act, establishes a framework for determining ownership interests in federally funded inventions. Under the Act, college and university, nonprofit, and small business federal contractors may "elect to retain title" to any invention conceived or reduced to practice in their performance of federally funded research. 35 U.S.C. 202(a). "If [the] contractor does not elect to retain title" to such an invention, the federal government may grant the inventor rights in the invention. 35 U.S.C. 202(d). The question presented is as follows:

Whether an inventor who is employed by a contractor that elects to retain rights in an invention may defeat the contractor's right to retain title under the Bayh-Dole Act by contractually assigning his putative rights in the invention to a third party.

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In the Supreme Court of the United States

No. 09-1159

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, PETITIONER

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING PETITIONER

INTEREST OF THE UNITED STATES

This case concerns the disposition of rights in federally funded inventions under the University and Small Business Patent Procedures Act of 1980, 35 U.S.C. 200 *et seq.*, commonly known as the Bayh-Dole Act. The United States spends billions of dollars per year on science and technology research at colleges and universities, other nonprofit organizations, and small businesses, and it therefore has a substantial interest in the resolution of this case. At the invitation of the Court, the United States filed a brief as amicus curiae at the petition stage of this case.

STATEMENT

1. The United States has long supported scientific and technological research by providing monetary grants to colleges and universities, other nonprofit organizations, and small businesses. Since 1980, the ownership of inventions resulting from that research has been governed by the University and Small Business Patent Procedures Act of 1980, 35 U.S.C. 200 *et seq.*, commonly known as the Bayh-Dole Act.

The Act establishes a comprehensive framework for the disposition of rights in federally funded inventions, specifically defining the rights of the research institutions, individual researchers, and the United States. Because the balance of interests set out in the Act is best understood in light of the history of ownership of federally funded inventions, this brief first sets out that history and then describes the provisions of the Act at issue here.

2. Before 1980, no uniform source of law governed ownership of inventions that resulted from federally funded research. Instead, a "melange of 26 different agency policies" determined who would own such inventions. H.R. Rep. No. 1307, 96th Cong., 2d Sess. Pt. 1, at 3 (1980) (*House Report*). Over time, two main approaches emerged: a "title" approach, under which title to a federally funded invention vested in the federal government by statute; and a "license" approach, under which the government allowed the recipient of federal funds to retain primary ownership rights in an invention, on the condition that it grant the government a license to use the invention.

For some federal agencies, statutes provided that title to patents on federally funded inventions automatically vested in the federal government unless the agency

waived its rights. See, *e.g.*, 42 U.S.C. 2182, 5908(a) (1976) (Department of Energy); 42 U.S.C. 2457(a) (1976) (National Aeronautics and Space Administration). By vesting title in the United States, those statutes superseded the inventor's common-law rights in his invention and his statutory patent rights. See *Arachnid, Inc.* v. *Merit Indus., Inc.*, 939 F.2d 1574, 1578 (Fed. Cir. 1991) (describing inventor's common-law and statutory rights). An inventor working on a federally funded project subject to those statutes therefore was not free to assign rights in his invention to third parties. Such an inventor had "no right to assign" because "when the invention was conceived by [the inventor], title to that invention immediately vested in the United States" by "operation of law." *FilmTec Corp.* v. *Hydranautics*, 982 F.2d 1546, 1550, 1553-1554 (Fed. Cir. 1992), cert. denied, 510 U.S. 824 (1993).

In contrast to agencies operating under vesting statutes, other agencies addressed ownership of patents for federally funded inventions by entering into agreements with individual research institutions that allowed those institutions to retain rights in such inventions. The National Science Foundation (NSF) and the Department of Health, Education and Welfare (HEW), for example, operated under Institutional Patent Agreement (IPA) programs adopted in the 1960s and 1970s. See David C. Mowery et al., *Ivory Tower and Industrial Innovation: University-Industry Technology Transfer Before and After the Bayh-Dole Act in the United States* 45 (2004). IPAs gave universities and nonprofit organizations with established technology-transfer programs a first option to own federally funded inventions. See S. Rep. No. 480, 96th Cong., 1st Sess. 21 (1979) (*Senate Report*). In return, those institutions typically were required to report

the invention to the government, grant the government a royalty-free license, refrain from charging excessive royalties to other licensees, use royalty income for the support of education or research, refrain from assigning rights except in limited circumstances, and take effective steps to commercialize the inventions. See, *e.g.*, Federal Council for Sci. & Tech., *Report on Government Patent Policy* 330-339 (HEW IPA), 340-353 (NSF IPA) (1976) (*Patent Policy Report*).

Experience with the vesting statutes and the IPA programs revealed that both had shortcomings. Under the vesting statutes, the government often lacked the resources to develop and commercialize patent rights obtained through federally funded research. Gov't Accountability Office, GAO-09-742, *Information on the Government's Right to Assert Ownership Control Over Federally Funded Inventions* 2 (2009) (*GAO Report*); *House Report* 1-2. As a result, only about five percent of federally funded inventions were being marketed commercially at the time the Bayh-Dole Act was enacted. See 126 Cong. Rec. 8739 (1980) (statement of Sen. Dole); *GAO Report* 2.

IPAs had a different but equally significant deficiency. The statutes governing several agencies, such as the NSF, prohibited the agencies from entering into contracts "inconsistent with any provision of law affecting the issuance or use of patents." 42 U.S.C. 1871(a) (1976). As a result, IPAs could not allocate ownership rights in federally funded inventions by their own force, but instead depended upon the university or nonprofit organization obtaining an assignment of rights from the researcher. See, *e.g.*, *Patent Policy Report* 330-331, 342. An institution's failure to obtain an effective assignment

of rights from the researcher thus could compromise the allocation of rights and obligations under the IPA. See, *e.g.*, *Government Patent Policy Act of 1980: Hearing on H.R. 5715 Before the Subcomm. on Science, Research and Technology of the H. Comm. on Science and Technology*, 96th Cong., 2d Sess. 80 (1980).

3. Congress enacted the Bayh-Dole Act to address those shortcomings. The Act establishes a uniform framework for the disposition of rights in federally funded inventions. That framework was designed to "use the patent system to promote the utilization of inventions arising from federally supported research or development," while "ensur[ing] that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions." 35 U.S.C. 200. Congress sought to balance the interests of the research institution, the government, and the inventor in a manner that would best "promote collaboration between commercial concerns and nonprofit organizations, including universities," and that would encourage "future research and discovery." *Ibid.*

The Act prescribes rights in "subject invention[s]," which are defined as "any invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement" between a contractor and a federal agency. 35 U.S.C. 201(e). A "contractor" is a "person, small business firm, or nonprofit organization that is a party to a funding agreement." 35 U.S.C. 201(c). The term "funding agreement" is broadly defined as "any contract, grant, or cooperative agreement entered into between any Federal agency, other than the Tennessee Valley Authority, and

any contractor for the performance of experimental, developmental, or research work funded in whole or in part by the Federal Government." 35 U.S.C. 201(b).

The Act creates a presumption that title to federally funded inventions will vest in the contractor, as opposed to the government or the inventor. That presumption is set out in the section of the Act titled "Disposition of rights," which states that a contractor may "elect to retain title to any subject invention." 35 U.S.C. 202(a). To exercise title, the contractor must "disclose each subject invention to the Federal agency within a reasonable time after it becomes known to contractor personnel responsible for the administration of patent matters." 35 U.S.C. 202(c)(1). The Act then requires the contractor to elect to retain title to the invention "within a reasonable time after disclosure," 35 U.S.C. 202(a), defined as "two years * * * or such additional time as may be approved by the Federal agency," 35 U.S.C. 202(c)(2), and to file timely patent applications for the invention, 35 U.S.C. 202(c)(3). The government "may receive title to any subject invention" when the contractor does not timely disclose the invention, elect to retain title, or seek patent protection for the invention. 35 U.S.C. 202(c)(1)-(3).

The contractor's title to a federally funded invention is subject to several additional conditions. If the contractor is a nonprofit organization, it must obtain federal agency approval before assigning rights in a subject invention, 35 U.S.C. 202(c)(7)(A); must "share royalties with the inventor," 35 U.S.C. 202(c)(7)(B); and must utilize the remaining royalties or income to further "scientific research or education," 35 U.S.C. 202(c)(7)(C). The contractor must also ensure that any assignee that is

granted the "exclusive right to use or sell any subject invention" agrees that any products made using the subject invention will be "manufactured substantially in the United States," unless the government waives that condition. 35 U.S.C. 204.

Although the Act presumptively vests title in the contractor, the government retains several important rights. The government is entitled to an irrevocable, paid-up license from the contractor to practice a federally funded invention. 35 U.S.C. 202(c)(4). Further, the government may keep title or otherwise restrict a contractor's title when particularly sensitive governmental interests are at stake, such as when a contractor is controlled by a foreign government or the research relates to foreign intelligence, nuclear propulsion, or nuclear weapons programs. 35 U.S.C. 202(a)(i)-(iv). The government also retains "march-in" rights to subject inventions, meaning that it may step in to license the invention in certain circumstances, such as when a contractor fails to take steps to achieve practical application of the invention, or when public health or safety requires it. 35 U.S.C. 203.

If a contractor does not elect to retain title to a subject invention, the federal agency "may consider"—"and after consultation with the contractor grant"—"requests for retention of rights by the inventor." 35 U.S.C. 202(d). The inventor's rights remain "subject to the provisions of this Act and regulations promulgated hereunder." *Ibid.*; see 37 C.F.R. 401.9. Thus, the inventor may receive title to the invention only when the contractor chooses not to retain title (or fails to comply with the applicable statutory prerequisites) and the government affirmatively authorizes the inventor to take title.

By its terms, the Bayh-Dole Act "take[s] precedence over any other Act which would require a disposition of rights in subject inventions of small business firms or nonprofit organizations contractors in a manner that is inconsistent with" the disposition of rights in the Act. 35 U.S.C. 210(a). Thus, unlike the pre-1980 experience with IPAs, when the ability of agencies like the NSF to control the allocation of rights in federally funded inventions was dependent on the contractor's obtaining an assignment of rights from the individual researcher, the Bayh-Dole Act explicitly gives precedence to the Act's own "[d]isposition of rights." 35 U.S.C. 202.

4. This case concerns the ownership of three patents for monitoring the effectiveness of treatments for human immunodeficiency virus (HIV). The patented process was developed by research scientists at the Leland Stanford Junior University (Stanford) using federal funds. One of those scientists, Dr. Mark Holodniy, performed research both at Stanford and at Cetus Corporation (Cetus). Holodniy executed agreements with both Stanford and Cetus regarding rights in his inventions, and a dispute subsequently arose about the ownership of the patents at issue here.

In the early to mid-1980s, Cetus developed polymerase chain reaction (PCR) technology, a technique for making billions of copies of specific sequences of DNA from a small number of starting molecules. Pet. App. 32a. In 1988, Cetus and Stanford began to collaborate on the use of PCR in HIV/AIDS research. *Ibid.* Later that year, Holodniy began to conduct research at Stanford's Center for AIDS Research. *Id.* at 34a-35a. Holodniy signed a "Copyright and Patent Agreement" with Stanford, *id.* at 118a-121a, in which he acknowledged that federal grants and contracts impose obliga-

tions on him with respect to federally funded inventions, *id.* at 118a; agreed to provide "a written disclosure" of any invention conceived or reduced to practice under a contract or grant, *id.* at 118a-119a; and "agree[d] to assign or confirm in writing to Stanford * * * that right, title and interest in * * * such inventions," *id.* at 119a.

In February 1989, Holodniy began to make regular visits to Cetus to learn about PCR and to develop a PCR-based test for HIV. Pet. App. 4a. At Cetus, Holodniy signed a "Visitor's Confidentiality Agreement," *id.* at 35a-36a, 122a-124a, in which he "assign[ed] to CETUS, [his] right, title, and interest in" any inventions conceived or reduced to practice "as a consequence of [his] access to CETUS' facilities or information," *id.* at 123a. Holodniy's research with Cetus produced an assay (procedure) for using PCR to measure the amount of HIV nucleic acids in blood samples from people infected with HIV. *Id.* at 5a, 37a. Holodniy published his findings with Cetus co-authors. *Ibid.*

Holodniy then returned to Stanford and conducted clinical studies to determine whether the assay could be used to judge the efficacy of anti-HIV drugs. Pet. App. 5a, 39a. That research demonstrated that PCR can be used to track the HIV RNA in a patient's bloodstream to assess the effectiveness of anti-HIV drugs the patient is taking. *Ibid.* Holodniy published this discovery with several Stanford and Cetus co-authors. *Id.* at 5a, 38a-40a. The research underlying the discovery was funded in part by the federal government through an agreement with Stanford. *Id.* at 5a, 109a, 114a-115a.

Beginning in 1992, Stanford submitted a series of patent applications for this method of monitoring the effectiveness of anti-HIV treatment, which resulted in the issuance of the three patents at issue. Pet. App.

107a-109a. Holodniy and other scientists are named as co-inventors of these patents, and Stanford is identified as the patent assignee. *Id.* at 4a, 125a, 127a, 129a, 131a; see *id.* at 41a (district court explains that Holodniy and other scientists "executed an assignment purporting to convey their interests in" the patents to Stanford and Stanford recorded the assignments with the Patent and Trademark Office). Each patent specified that the "invention was made with Government support" and that "[t]he Government has certain rights in th[e] invention." *Id.* at 5a-6a, 126a, 128a, 132a; see 35 U.S.C. 202(c)(6) (requiring such specifications). Stanford then disclosed the inventions to the federal government and confirmed to the government the grant of irrevocable, paid-up licenses to the inventions. Pet. App. 5a. In 1995, Stanford formally elected to retain title to the inventions under the Bayh-Dole Act. *Id.* at 5a-6a, 115a-116a.

5. Ten years later, petitioner filed suit, alleging that respondents (who had purchased Cetus's PCR business) were marketing HIV detection kits that infringed its patents. Pet. App. 5a-6a, 31a. Respondents counterclaimed, contending, *inter alia*, that they possessed ownership interests in the patents because of Holodniy's agreement with Cetus. *Id.* at 6a-7a, 122a-124a.

The district court rejected respondents' claim of ownership on several grounds. As relevant here, the court held that Holodniy's assignment to Cetus was ineffective to convey an interest in the patents because, under the Bayh-Dole Act, he lacked any such interest to convey. Pet. App. 61a-62a. The court explained that when "the individual inventor is not a contracting party," "the Bayh-Dole Act provides that the individual inventor may obtain title only after the government and the contracting party have declined to do so." *Id.* at 61a

(citing 35 U.S.C. 202(d)). Because "Stanford exercised its right and obtained title in the patents" under the Bayh-Dole Act, the court concluded, Holodniy "had no interest to assign to Cetus." *Id.* at 62a.

In a later proceeding, the district court held that the patents were invalid for obviousness. See *Board of Trs. of Leland Stanford Junior Univ.* v. *Roche Molecular Sys., Inc.*, 563 F. Supp. 2d 1016, 1039-1049 (N.D. Cal. 2008). Petitioner appealed that decision, and respondents cross-appealed on the ownership issue. Pet. App. 2a-3a.

6. The court of appeals affirmed in part, vacated in part, and remanded. Pet. App. 1a-28a. As relevant here, the court held that petitioner had obtained no ownership interests in the patents from Holodniy because Holodniy had assigned his patent rights to Cetus, leaving nothing for him to assign to Stanford. *Id.* at 27a-28a. The court regarded the contract between Holodniy and Stanford, in which Holodniy "agree[d] to assign or confirm in writing" any invention he conceived or reduced to practice while at Stanford, as merely a promise to assign his rights "to Stanford at an undetermined time." *Id.* at 13a. By contrast, the court viewed Holodniy's agreement with Cetus—in which Holodniy stated that he "will assign *and do[es] hereby assign* to CETUS" his interest in inventions conceived as a consequence of his access to Cetus facilities and information—as "effect[ing] a present assignment" to Cetus of his future inventions. *Id.* at 14a (emphasis added). The court concluded that "Cetus's legal title vested first" and that Holodniy therefore had no rights to assign to Stanford with respect to the pertinent invention. *Ibid.*

The court of appeals rejected petitioner's contention that the Bayh-Dole Act gave Stanford title to the pat-

ents. Pet. App. 18a-21a. In the court's view, the Bayh-Dole Act was relevant only to determine what residual rights Stanford and the government might have after effectuating the assignments in the Holodniy-Stanford and Holodniy-Cetus agreements. *Id.* at 19a-20a; see *id.* at 21a. The court stated that "Stanford was entitled to claim whatever rights were still available after the Government declined to exercise its option [to take title to the patents], including the rights of [Holodniy's co-inventors on the patents]." *Id.* at 19a. But the court determined that Stanford could not claim title to the patents because Holodniy "still possessed rights at the time he signed the [agreement] with Cetus"; he assigned those rights to Cetus in the agreement; and the Act did not "automatically void the patent rights that Cetus received from Holodniy." *Id.* at 19a, 21a.

The court of appeals concluded that petitioner lacked standing to pursue the infringement claim because it did not own Holodniy's interest in the patents and, under Federal Circuit precedent, all co-owners must join as plaintiffs in an infringement suit. Pet. App. 27a. Based on that determination, the court vacated the district court's judgment that the patents were invalid. *Id.* at 27a-28a.

SUMMARY OF ARGUMENT

The Bayh-Dole Act permits a college or university, nonprofit organization, or small business contractor to retain patent rights in an invention conceived of or reduced to practice using federal funds. An individual inventor employed by the contractor may not defeat the contractor's presumptive title by assigning his putative rights to a third party.

A. The Act establishes a comprehensive framework for the "[d]isposition of rights" in federally funded inventions. 35 U.S.C. 202. That framework gives a contractor first priority by allowing it to "elect to retain title" to any subject invention. 35 U.S.C. 202(a). The federal government occupies the next position in the hierarchy: it has the right to a paid-up license and the ability to grant licenses as necessary to ensure commercialization, and it may take title to the invention if the contractor declines to exercise its rights or if important national interests require it. 35 U.S.C. 202(a) and (c)(1)-(4), 203. The inventor has lowest priority: he may retain title only if the contractor forfeits its rights and the government affirmatively authorizes him to retain title. 35 U.S.C. 202(d).

The court of appeals erred in allowing an individual inventor to circumvent through private contract the Bayh-Dole Act's framework for allocating ownership of federally funded inventions. Stanford complied with all of the requirements to obtain title under the Act, yet the court determined that Holodniy had compromised Stanford's rights by assigning ownership of the inventions to Cetus. That was error because Holodniy had no ownership rights in the subject inventions to assign to Cetus. And nothing in the Bayh-Dole Act suggests that a contractor must obtain an assignment of rights from an inventor to retain clear title under the Act.

B. The Act's history confirms that it is intended to grant contractors presumptive ownership of federally funded inventions by operation of law. Before 1980, title to federally funded inventions generally vested in the government by statute or could be retained by contractors by contract. In enacting the Act, Congress chose to allocate primary ownership rights to contractors in or-

der to best encourage commercialization of useful inventions. Both supporters and opponents of the Act understood that it gave first priority to contractors so long as they followed the steps set out in the Act. The legislative history confirms that an individual inventor can obtain (and thus can assign) ownership rights in a federally funded invention only if the contractor declines to exercise its rights under the Act and the government authorizes the inventor to take title.

C. The court of appeals' decision frustrates the Act's important purposes. By allowing an inventor conducting federally funded research to override the Act's allocation of rights, the decision below undermines the uniformity and certainty of title that is necessary for effective commercialization. Moreover, the court of appeals' rule frustrates the government's ability to protect the taxpayers' multi-billion-dollar investments in research and development by allowing an inventor to transfer ownership of an invention to a third party that is not subject to the government's licensing and march in rights. Finally, the decision below allows an inventor to nullify the provisions of the Act that require royalties to be dedicated to further research and development and products using the invention to be made in the United States, further reducing the Act's intended benefit to the public.

ARGUMENT

AN INDIVIDUAL INVENTOR MAY NOT DEFEAT A CONTRACTOR'S ELECTION OF TITLE UNDER THE BAYH-DOLE ACT BY ASSIGNING HIS PUTATIVE RIGHTS IN AN INVENTION TO A THIRD PARTY

The Bayh-Dole Act establishes a comprehensive framework for allocating rights in federally funded inventions. Under that framework, a contractor has pre-

sumptive title to a subject invention so long as the contractor complies with enumerated statutory prerequisites. The court of appeals' decision allows an individual inventor to defeat the contractor's title by assigning rights to a third party outside the framework of the Act. That holding cannot be reconciled with the Act's text, history, and purposes.

A. The Bayh-Dole Act Establishes A Comprehensive Framework For The Disposition Of Rights In Federally Funded Inventions

1. By its plain terms, the Act sets out a framework for the "[d]isposition of rights" in federally funded inventions. 35 U.S.C. 202(a). The Act establishes a statutory hierarchy of rights among contractors, the government, and inventors, and it specifically defines the circumstances under which each may take title to a federally funded invention.

First priority in this statutory scheme belongs to the contractor. The Act states that a contractor "may * * * elect to retain title to any subject invention." 35 U.S.C. 202(a). That statement—the first allocation of rights contained in the Act—makes clear that title to a subject invention presumptively vests in the research institution where the invention was developed using federal funds. See, *e.g.*, *Senate Report* 31 (the "normal rule" under the Act is that "small business firms and nonprofit organizations are to have the right to elect to retain worldwide ownership of their inventions"). If the contractor wishes to own and develop the invention, all it must do is "elect" to retain title and comply with the further conditions for exercising title set out in the Act, *i.e.*, the obligations to disclose the invention, to make an election of title, and to seek patent protection in a timely

manner. 35 U.S.C. 202(c)(1)-(3). The Act does not condition the contractor's title to an invention on an assignment of rights from an inventor, but instead grants the contractor presumptive title to the invention by operation of law.

The Act further provides that the government retains important rights in federally funded inventions owned by the contractor and may, in some circumstances, take title to a subject invention. When the contractor elects to retain title to an invention, the government has the right to "a nonexclusive, nontransferable, irrevocable, paid-up license" to practice the invention, 35 U.S.C. 202(c)(4), and has the authority to require the contractor, its assignee, or an exclusive licensee to license the invention in order to achieve practical application of it, 35 U.S.C. 203. In addition, the government may take title to an invention if the contractor does not notify the government of the invention, does not elect to retain title to the invention, or does not seek patent protection for the invention in a timely manner. 35 U.S.C. 202(c)(1)-(3). In certain circumstances, such as when the research to be performed implicates particularly sensitive government interests, the government may provide in the funding agreement with the contractor that title to any resulting inventions will vest in the government. 35 U.S.C. 202(a). But the contractor's decision to retain title controls unless the government has retained title through a funding agreement or the contractor fails to exercise its rights in the manner and within the time specified in the Act.

The Act also confers limited rights on individual inventors of subject inventions. A nonprofit contractor that retains title under the Act must "share royalties with the inventor." 35 U.S.C. 202(c)(7)(B). The Act fur-

ther provides that, if a contractor declines to retain title (or fails to exercise its rights under the Act), the government funding agency "may consider and after consultation with the contractor grant requests for retention of rights by the inventor." 35 U.S.C. 202(d). In that circumstance, the inventor obtains title to the invention "subject to the provisions of th[e] Act and regulations promulgated [t]hereunder." *Ibid.*; see 37 C.F.R. 401.9. Thus, with respect to ownership of patent rights in federally funded inventions, the inventor's rights are subordinate to those of both the contractor and the federal government. See, *e.g.*, *Platzer* v. *Sloan-Kettering Inst. for Cancer Research*, 787 F. Supp. 360, 364-365 (S.D.N.Y.) (concluding that "the intended beneficiaries of the Bayh-Dole Act are the [research] institutions themselves and the government," not the inventors), aff'd, 983 F.2d 1086 (Fed. Cir. 1992) (unpublished; per curiam), cert. denied, 507 U.S. 1006 (1993).

2. In this case, Stanford retained title to the inventions at issue by complying with the Bayh-Dole Act. The court of appeals did not question Stanford's contention that the inventions at issue are "subject inventions" within the meaning of the Act. To the contrary, the court stated that the results of research conducted by Holodniy and other researchers at Stanford "formed the basis for the patents-in-suit," Pet. App. 6a, and it held that Holodniy's prior assignment to Cetus would control "[e]ven if Holodniy conceived and reduced to practice [the invention] after departing Cetus," *id.* at 15a. And the record makes clear that the pertinent research at Stanford was funded in part by two federal grants for AIDS research. *Id.* at 109a, 114a-115a.

Accordingly, when the inventions were made, title presumptively vested in Stanford by operation of law. 35 U.S.C. 202(a). Stanford then took the steps required to exercise its title: it disclosed the inventions to the government and provided to the government paid-up licenses to practice the inventions, Pet. App. 5a-6a, 114a-116a; see 35 U.S.C. 202(c)(1) and (4); submitted patent applications for the inventions, Pet. App. 5a, 108a-109a; see 35 U.S.C. 202(c)(3); and provided to the government a formal written election to retain title to the inventions, Pet. App. 5a-6a, 115a-116a; see 35 U.S.C. 202(a) and (c)(2). Indeed, neither the court of appeals nor respondent has disputed that Stanford took the necessary steps under the Act in order to exercise title to the inventions.

3. The court of appeals erred by failing to enforce the "[d]isposition of rights" (35 U.S.C. 202) in the inventions mandated by the Bayh Dole Act, and by instead treating Stanford's rights in the inventions as depending upon Holodniy's assignment of title. That approach was incorrect because the Act allows a contractor to retain title by operation of law, 35 U.S.C. 202(a), and the inventor may gain title to the invention only when the contractor forfeits its right to title, 35 U.S.C. 202(d). Here, Holodniy possessed a contingent interest in any patentable "subject invention" that he might create with the assistance of federal funds, one that would mature only if the contractor waived or failed to exercise its rights under the Act and the government then authorized Holodniy to retain title. Although nothing in the Bayh-Dole Act precluded Holodniy from assigning that contingent interest to Cetus, Holodniy could not assign to Cetus any higher priority in the federally funded inventions than Holodniy himself would have possessed. Be-

cause Stanford elected to retain title under the Act, Holodniy's prior assignment did not have the effect of conveying to Cetus an ownership interest that Holodniy could not have asserted.[1]

The court of appeals framed the question presented as whether Stanford's "election of title under Bayh-Dole had the power to void any prior, otherwise valid assignments of patent rights." Pet. App. 19a. Stanford's entitlement to retain title to the patented inventions, however, does not depend on the view that the Bayh Dole Act "void[ed]" Holodniy's assignment of rights to Cetus. Holodniy assigned to Cetus *his own* "right, title, and interest in" any inventions conceived or reduced to practice "as a consequence of [his] access to CETUS' facilities or information," *id.* at 123a; but the parties to that agreement surely understood that the scope of Holodniy's rights in any later-developed inventions would be determined under applicable law. If Holodniy's eventual contributions to the research that produced the patented inventions had not justified treating him as a co-inventor, for example, Cetus would have acquired no rights in those inventions because Holodniy would have had no such rights to assign. Similarly here, the Bayh-Dole Act did not "void" Holodniy's assignment to Cetus of all his rights in the relevant inventions; it simply limited, to the contingent interests described above, the rights that Holodniy could potentially assign.

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[1] The Act requires a nonprofit organization that retains title to a federally funded invention to share any royalties with the inventor, 35 U.S.C. 202(c)(7)(B), and nothing in the Act would have precluded Holodniy from assigning to Cetus all or part of his contingent interest in such royalties. Neither the parties nor the courts below have suggested, however, that any such royalties are in dispute.

By placing the disposition of rights in a federally funded invention in the hands of the inventor, the court of appeals turned the Bayh-Dole Act's hierarchy on its head. In the court's view, title to a federally funded invention belongs in the first instance not to the contractor, but to the inventor. The court determined that Holodniy possessed rights in the inventions that he had assigned to Cetus, Pet. App. 19a, and that Stanford's and the government's rights were subordinate to Holodniy's assignment, *id.* at 13a 18a. The court considered the government's rights second, stating that "when the Bayh-Dole Act's provisions are violated, 'the government can choose to take action * * * [but] title remains with the named inventors or their assignees.'" *Id.* at 18a-19a (quoting *Central Admixture Pharmacy Servs., Inc.* v. *Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347, 1352-1353 (Fed. Cir.), cert. denied, 552 U.S. 1038 (2007)). The court put the contractor's rights last, stating that Stanford could only "claim whatever rights were still available after the Government declined to exercise its option." *Ibid.*

As a result, the court held that an inventor like Holodniy may preclude a university or other nonprofit contractor from obtaining its statutory ownership interests in a federally funded invention simply by making a present assignment of rights to a third party. That holding nullifies the university or other nonprofit contractor's statutory right to elect to retain title, as well as its corresponding statutory obligations to commercialize the invention, grant the government a license, and devote the proceeds to research and education.

4. The Bayh-Dole Act allows a contractor to obtain clear title to an invention by operation of law, without seeking any assignment by an inventor. The Act states

that the contractor may "elect to retain title" in a subject invention, 35 U.S.C. 202(a), and it describes that election as the contractor's "acquir[ing] title under this chapter," 35 U.S.C. 203(a), and "receiv[ing] title to a[] subject invention," 35 U.S.C. 204. The Act specifies the steps the contractor must take to exercise title under the Act (35 U.S.C. 202(c)(1)-(3)), and those steps do not include the acquisition of an assignment of rights from the inventor. Regulations implementing the Bayh-Dole Act confirm that, when a contractor complies with the statutory requirements, it "retain[s] the entire right, title, and interest throughout the world to each subject invention." 37 C.F.R. 401.3(a); see 37 C.F.R. 401.14(a) (clause (b)).

Contrary to the court of appeals' understanding (Pet. App. 19a), title to a "subject invention" within the meaning of the Bayh-Dole Act does not initially vest in the inventor. To be sure, under the Patent Act, the right to obtain a patent on an invention generally belongs to the inventor, who may assign that right. See 35 U.S.C. 101, 115, 116, 152. By its terms, however, the Bayh-Dole Act "take[s] precedence over any other Act" governing the disposition of rights in subject inventions. 35 U.S.C. 210(a). Thus, even assuming that Holodniy's assignment of rights to respondent would otherwise have prevailed over his assignment of rights to petitioner, the priority rules in the Bayh-Dole Act are controlling here.[2]

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[2] Respondent suggests (Supp. Cert. Br. 12) that the Bayh-Dole Act does not displace an inventor's rights under the Patent Act because Section 210 does not specifically mention the Patent Act. But the Bayh-Dole Act states that it takes precedence over "*any* other Act" that would require a contrary disposition of rights, "including *but not necessarily limited to*" the 21 listed statutes. 35 U.S.C. 210(a) (emphasis added). Because "statutory language suggesting exclusive

The Act's specification of the circumstances in which an inventor may retain title to a subject invention confirms that the inventor does not have the initial right to title under the Act. An inventor may retain rights in a subject invention only if "a contractor does not elect to retain title" and the government grants the inventor's request for retention of rights after consulting with the contractor. 35 U.S.C. 202(d); see 37 C.F.R. 401.9 (inventor's ability to retain title is subject to federal approval). The Act does not identify any other circumstance in which an inventor can obtain title, and it does not allow an inventor to trump the rights of a contractor. See, *e.g.*, *Fenn* v. *Yale Univ.*, 393 F. Supp. 2d 133, 139 (D. Conn. 2004) (inventor could not retain rights under Act where university intended to exercise right to retain title and informed the government of that intention), aff'd, 184 Fed. Appx. 21 (2d Cir. 2006) (unpublished opinion).

That conclusion is reinforced by the Act's restrictions on inventors who *are* allowed to retain rights in subject inventions. The Act provides that, "[i]f a contractor does not elect to retain title to a subject invention" and the government "grant[s] [a] request[] for retention of rights by the inventor," the inventor takes title "subject to the provisions of [the Bayh-Dole] Act and regulations promulgated [t]hereunder." 35 U.S.C. 202(d). The applicable regulations in turn state that, when an inventor is allowed "to retain rights to a subject invention" pursuant to Section 202(d), the agency must impose upon the

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ness is missing," *Chevron U.S.A. Inc.* v. *Echazabal*, 536 U.S. 73, 81 (2002), respondent's invocation of the *expressio unius* canon is inapt; and because Section 210 does not provide "a list of specific items followed by a general term," *Hall St. Assocs.* v. *Mattel, Inc.*, 552 U.S. 576, 586 (2008), the *ejusdem generis* canon is likewise inapposite.

inventor specified restrictions that apply to small business contractors. 37 C.F.R. 401.9.

The Act does not expressly limit the prerogatives of an inventor who obtains rights in a subject invention *other than* pursuant to Section 202(d). The natural inference from that omission is that inventors can obtain such rights only if the contractor declines to retain title and the government grants the inventor's request. By contrast, the court of appeals' decision suggests that inventors can exercise *greater* rights in subject inventions outside of the Bayh-Dole Act framework than they could exercise after satisfying the statutory prerequisites to retention of title. That approach would seriously undermine Congress's effort to ensure that federally funded inventions are used to advance the public interest.[3]

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[3] Congress's authority to allocate inventors' rights in federally funded inventions is reinforced by long standing practice regarding patentable inventions created by federal employees. A 1950 Executive Order, which remains in effect today, provides that "[t]he Government shall obtain the entire right, title and interest in and to all inventions made by any Government employee (1) during working hours, or (2) with a contribution by the Government of facilities, equipment, materials, funds, or information, or of time or services of other Government employees on official duty, or (3) which bear a direct relation to or are made in consequence of the official duties of the inventor." Exec. Order No. 10,096, 3 C.F.R. 292 (1949-1953 Comp.), amended by Exec. Order No. 10,695, 3 C.F.R. 355 (1954-1958 Comp.), and Exec. Order No. 10,930, 3 C.F.R. 456 (1959-1963 Comp.). Federal regulations implement that policy and provide detailed procedures for employees to retain title to inventions that were made outside the course of their federal work. See 37 C.F.R. Pt. 501. Just as the government may allocate rights in inventions made by its employees, see, *e.g.*, *Heinemann* v. *United States*, 796 F.2d 451, 455-456 (Fed. Cir. 1986), cert. denied, 480 U.S. 930 (1987), it may also allocate rights in inventions made by its contractors with federal funds.

B. The Bayh-Dole Act's History Confirms That An Inventor May Not Trump A Contractor's Election Of Rights By Private Contract

1. Before 1980, there was significant debate throughout the federal government about whether it would best serve the public interest to vest title to federally funded inventions in the government or to grant ownership to the research institutions where the inventions were made. Pet. Br. 2-10; see pp. 2-5, *supra*. In the Bayh-Dole Act, Congress granted primary rights in federally funded inventions to the research institutions, rather than to the government. The congressional deliberations evidenced an overriding concern that, although the government was spending significant sums on science and technology research, taxpayers were not gaining useful products in return. The Senate Report accompanying the Act noted the "inability of the Federal agencies to deliver new inventions and processes from their research and development programs to the marketplace where they can benefit the public," *Senate Report* 2, primarily due to resource constraints, *id.* at 19 (citing statistic that "the cost of taking a new invention from basic research through development and commercialization costs 10 times as much as did the basic research itself").

Although federal agencies that owned patents generally "ma[de] them available to private businesses for development and possible commercialization through nonexclusive licenses," that approach had proved inadequate to encourage private industry to take on the substantial costs of bringing a product to market. *Senate Report* 2; see *id.* at 18. As a result, "[h]undreds of valuable medical, energy, and other technological discoveries [we]re sitting unused under Government control,"

126 Cong. Rec. at 8739 (statement of Sen. Bayh), and "the public [wa]s not receiving the full benefits of the research and development efforts that it [wa]s supporting," *Senate Report* 19.

Congress chose to allow universities and other contractors to retain title to those inventions because it viewed those entities as better positioned than the federal agencies to develop federally funded inventions. Extensive hearings had "clearly demonstrated that the universities and nonprofit organizations who are conducting this research effort are much more efficient in delivering these important discoveries to the marketplace than are the [federal] agencies." *Senate Report* 29. Congress therefore granted those contractors the exclusive ownership rights required for effective commercialization of the inventions, *id.* at 3, 18, 24, while giving the federal government a license to use the inventions, *id.* at 30. Congress further sought to "protect [the] public welfare" by giving the government march-in rights to license any federally funded invention that the relevant contractor was not adequately utilizing. *Id.* at 28.

2. The legislative record reflects a consensus that, under the statute as ultimately enacted, a contractor could obtain clear title to a federally funded invention by complying with the conditions set out in the Act. Section 202 of the Act "establishe[d] the basic framework for the disposition of rights in inventions made by small business firms and nonprofit organizations under funding agreements with the Federal Government." *Senate Report* 31. Under that framework, the "normal rule" is that "small business firms and nonprofit organizations are to have the right to elect to retain *worldwide ownership* of their inventions by making an election within a

reasonable time after they disclose the invention." *Ibid.* (emphasis added). See, *e.g.*, 126 Cong. Rec. at 8741 (statement of Sen. Nelson) (Act "establish[es] a presumption that universities and small businesses shall retain title to inventions they develop with government financial assistance"); *id.* at 2007 (statement of Sen. Weicker) (Act "grant[s] to the universities and small companies the right of first refusal for patents arising from their Federal grants or contracts"); *The University and Small Business Patent Procedures Act: Hearings on S. 414 Before the Sen. Comm. on the Judiciary*, 96th Cong., 1st Sess. 40 (1979) (statement of Elmer Staats, Comptroller General of the United States) (statute embodies "a uniform Government-wide title-in-the-contractor policy"); *House Report* 5 (similar House bill "establishes a presumption that ownership of all patent rights in government funded research will vest in [the] contractor")[4]; see also *Statement on Signing H.R. 6933 Into Law*, 16 Weekly Comp. Pres. Doc. 2803, 2804 (Dec. 12, 1980) ("[T]his legislation enables small businesses and nonprofit organizations to obtain title to inventions made with Federal support.").

It was well understood that the Act would "automatically grant small businesses and nonprofits title to inventions arising from Government-supported research." *Senate Report* 36 (statement of Alice Rivlin, Director of the Congressional Budget Office). See, *e.g.*, *House Report* 12 (similar House bill "provides for the acquisition

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[4] Although the *House Report* considered an earlier version of the bill, which provided that "[a] contractor that is a small business or a nonprofit organization will acquire title to its contract invention," 126 Cong. Rec. at 29,891, there is no suggestion in the legislative record that Members of Congress viewed that language as materially different from the language that ultimately was enacted.

of title to contract inventions by contractors which are either a small business or a nonprofit organization"). Even those Members of Congress who disagreed with the balance of interests struck in the Act understood that it "assigns *automatic title* to the contract invention where the contractor is a small business or nonprofit organization." *Id.* at 30 (views of Rep. Brooks) (emphasis added).

3. At no point before or during the debates on the Bayh-Dole Act did any widely-held view emerge that an individual inventor should retain ownership rights in a federally funded invention. In the decades before the Act's passage, the government either allowed research institutions to retain ownership of federally funded inventions or kept the inventions for itself. See pp. 2-5, *supra*. Neither of those approaches allowed individual inventors to retain title to federally funded inventions. In enacting the Bayh-Dole Act, Congress chose the former approach over the latter; it did not choose an unprecedented third option in which an individual inventor could assign away rights in a subject invention contrary to the wishes of both the contractor and government. Indeed, those Members of Congress who objected to the disposition of rights mandated by the Act did so because they believed that the government should have greater rights in subject inventions than contractors—not because they believed inventors should have ownership rights. See, *e.g.*, *House Report* 29 (views of Rep. Brooks) (asserting that "what the government acquires through the expenditure of its citizens' taxes, the government owns," and describing the statute as "a pure giveaway of rights that properly belong to the people"); 126 Cong. Rec. at 8738 (statement of Sen. Long) (statute

would give contractors "gifts of ownership of taxpayer-financed research").[6]

4. The legislative record does not suggest that a contractor's election of title would be effective only if the contractor obtained an assignment of rights from the inventor. Rather, the Committee Reports describe the inventor's ability to take title to a federally funded invention as contingent on the contractor's declining to take title. See, *e.g.*, *Senate Report* 33 (Section 202(d) "provides agencies with the authority to leave rights with individual inventors in cases when contractors do not elect rights"); *House Report* 16 (similar House bill "authorized a contractor's employee-inventor to receive some or all of the contractor's rights to a contract invention if the responsible agency and the contractor approve"). That omission is telling because, under the IPAs previously used by some agencies, the contractor was required to obtain such an assignment because the agencies themselves lacked statutory authority to allocate the inventor's rights. See pp. 3-5, *supra*. Congress did possess that authority, however, and it decided to "override conflicting statutes" so that its policy of granting ownership rights to a contractor would be "uniform." *Senate Report* 26.

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[6] Some Members of Congress suggested that the statute "does not go far enough" and that "all contractors, regardless of size or profit status," should be able "to acquire title to their inventions made under Federal contracts." 126 Cong. Rec. at 30,365 (statement of Sen. Schmitt); see also, *e.g.*, *id.* at 8745-8746 (statement of Sen. Cannon); 1993-1994 (statement of Sen. Stevenson). That view eventually was reflected in Executive Order No. 12,591, 3 C.F.R. 220 (1987 Comp.), which instructed federal agencies to apply portions of the Bayh-Dole Act to large contractors. See also *Memorandum on Gov't Patent Policy*, 1 Pub. Papers 248 (Feb. 18, 1983).

C. Allowing An Inventor To Transfer Ownership Of A Federally Funded Invention Outside The Bayh-Dole Act's Framework Frustrates Congress's Purposes

Congress enacted the Bayh-Dole Act to "promote the utilization of inventions arising from federally supported research or development"; to "ensure that the Government obtains sufficient rights" in federally funded inventions to protect taxpayers' investments; to encourage "future research and discovery"; and to benefit "United States industry and labor." 35 U.S.C. 200. The court of appeals' decision frustrates each of those important purposes.

1. The Act's primary purpose was to encourage commercialization by bringing uniformity and certainty to ownership of federally funded inventions. *Senate Report* 1-3. Since 1980, contractors have understood that, if they comply with the Act's requirements, they can obtain title to federally funded inventions subject to certain rights retained by the government. See *The Bayh-Dole Act—The Next 25 Years: Hearing Before the Subcomm. on Technology and Innovation of the H. Comm. on Science and Technology*, 110th Cong., 1st Sess. 4-5 (2007); Pet. App. 111a, 137a (reflecting Stanford's understanding).[6] That certainty of title has been

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[6] See also, *e.g.*, Michael S. Mireles, Jr., *States As Innovation System Laboratories: California, Patents, and Stem Cell Technology*, 28 Cardozo L. Rev. 1133, 1143 (2006) ("The Act provides a presumption of ownership in the recipient of the grant funding."); Gary Pulsinelli, *Share and Share Alike: Increasing Access to Government-Funded Inventions Under the Bayh-Dole Act*, 7 Minn. J. L. Sci. & Tech. 393, 403 (2006) (Act "allow[s] [contractors] to retain title to the inventions if they diligently file patent applications and promote commercial development of the inventions"); John H. Raubitschek, *Responsibilities Under the Bayh-Dole Act*, 87 J. Pat. & Trademark Off. Soc'y 311, 311

a driving factor behind the massive increase in patents by United States colleges and universities. See, *e.g.*, *Innovation's Golden Goose*, The Economist, Dec. 14, 2002, at 3 (calling the Act "the most inspired piece of legislation to be enacted in America over the past half-century" and documenting sharp rise in patents and jobs created); AAU Cert. Br. 2, 16-20; MIT Cert. Br. 7-10. Moreover, "the assurance of clear title to Government-funded inventions provided by the Act has led directly to increased patent licensing," which "has been a major factor in allowing increased business support and collaboration in university research." S. Rep. No. 662, 98th Cong., 2d Sess. 2 (1984). "Universities can negotiate with businesses and reach agreements over who will have what rights to inventions that come from joint efforts when the universities own the basic patents." *Ibid.*

The court of appeals' decision upsets the settled expectations of the nation's federally funded research institutions. Under the decision below, even when a contractor elects to retain title and complies with the requirements of the Act, an inventor may defeat that title by making an assignment to a third party, the terms or even existence of which may be unknown to the contractor at the time of the election and for years thereafter. The decision below thus creates serious uncertainty about contractors' title to patents, raising the cost of due diligence for contractors and potential licensees, and making it difficult and risky for contractors to give po-

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(2005) (Act "gave universities and small businesses the right to own their inventions made with federal funds"); *Innovation's Golden Goose*, The Economist, Dec. 14, 2002, at 3 ("[The Act] transferred ownership of an invention or discovery from the government agency that had helped to pay for it to the academic institution that had carried out the actual research.")

tential licensees or investors warranties of good title to patents obtained through the Bayh-Dole Act framework.

Contractors and the government cannot limit the damage to the Bayh-Dole Act scheme by modifying their assignment clauses in future contracts. Changing future contracts will not change the allocation of rights for the massive number of past and present agreements relating to ongoing or completed research over the three decades since the Act took effect. See Pet. 17-18. And even with respect to future contracts between universities and individual researchers, a university that insisted upon a present assignment of rights from the researcher would still run the risk that the researcher had already executed a similarly worded assignment of rights to a third party, and that the earlier assignment would be found controlling.

2. The decision below also impairs the government's ability to protect taxpayers' substantial investment in scientific research and development. The federal government funds over half of all scientific and technical research conducted at colleges and universities in the United States, see *GAO Report* 1, which amounted to more than $31 billion in 2008, NSF, *NSF 10-311, Academic R&D Expenditures: FY 2008*, at 8 & tbl. 1 (2010). Additional billions of dollars of federal funds are provided each year to small businesses and nonprofit organizations.

Congress recognized that the federal government should have the authority to protect those substantial investments and ensure that taxpayers benefit from them. *Senate Report* 16 (recognizing the need to "receive the optimum return on the Federal Government's basic research expenditures since this is becoming by far the largest source of American basic research

money"). Accordingly, the Bayh-Dole Act guarantees the government an irrevocable, paid-up license from the contractor to practice a federally funded invention. 35 U.S.C. 202(c)(4). The Act further provides that, if a contractor does not take sufficient action to achieve practical application of the invention, is not adequately satisfying a public health or safety need related to the invention, or has not ensured that assignees with exclusive rights manufacture products using the invention substantially in the United States, the agency may "march in" and require the contractor to grant licenses to third parties. 35 U.S.C. 203, 204. Those provisions give the government "leverage to promote commercialization of federally funded inventions." *GAO Report* 9-12. By allowing an inventor to assign rights in federally funded inventions free from the restrictions that bind the contractor, and that would similarly bind the inventor himself if he took title under the Bayh-Dole framework after the contractor declined to do so, the court of appeals' decision subverts Congress's effort to ensure that federal funding for research ultimately promotes the public interest. See pp. 20, 22-23, *supra*.

3. Allowing an inventor to transfer ownership of a federally funded invention to a third party would similarly frustrate Congress's efforts to foster scientific research and development in the United States and to benefit American workers. Congress required that nonprofit contractors use "the balance of any royalties or income earned * * * for the support of scientific research or education," 35 U.S.C. 202(c)(7)(C), not only to "assist * * * the university or nonprofit organization" in its further research efforts, but to bring "very real benefit[s] to the public." *Senate Report* 30. Congress also required that a contractor obtaining title under the

Act must ensure that any assignee granted the "exclusive right to use or sell any subject invention" agrees to manufacture any products using the subject invention "substantially in the United States" unless the government waives that condition, 35 U.S.C. 204. That preference for United States industry "is designed to maximize the probability that the jobs created through the commercialization of new products and technologies based on Government supported inventions will benefit American workers." *Senate Report* 34. Under the decision below, however, an inventor may evade those requirements by assigning rights in a federally funded invention to a third party outside of the Bayh-Dole Act framework. It is only through the comprehensive scheme set out in the Act that Congress's objectives can be realized.

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted.

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APPENDIX

1. 35 U.S.C. 200 provides:

Policy and objective

It is the policy and objective of the Congress to use the patent system to promote the utilization of inventions arising from federally supported research or development; to encourage maximum participation of small business firms in federally supported research and development efforts; to promote collaboration between commercial concerns and nonprofit organizations, including universities; to ensure that inventions made by nonprofit organizations and small business firms are used in a manner to promote free competition and enterprise without unduly encumbering future research and discovery; to promote the commercialization and public availability of inventions made in the United States by United States industry and labor; to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions; and to minimize the costs of administering policies in this area.

2. 35 U.S.C. 201 provides:

Definitions

As used in this chapter—

(a) The term "Federal agency" means any executive agency as defined in section 105 of title 5, and the military departments as defined by section 102 of title 5.

(b) The term "funding agreement" means any contract, grant, or cooperative agreement entered into between any Federal agency, other than the Tennessee Valley Authority, and any contractor for the performance of experimental, developmental, or research work funded in whole or in part by the Federal Government. Such term includes any assignment, substitution of parties, or subcontract of any type entered into for the performance of experimental, developmental, or research work under a funding agreement as herein defined.

(c) The term "contractor" means any person, small business firm, or nonprofit organization that is a party to a funding agreement.

(d) The term "invention" means any invention or discovery which is or may be patentable or otherwise protectable under this title or any novel variety of plant which is or may be protectable under the Plant Variety Protection Act (7 U.S.C. 2321 *et seq.*).

(e) The term "subject invention" means any invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement: *Provided*, That in the case of a variety of plant, the date of determination (as defined in section 41(d)[1] of the Plant Variety Protection Act (7 U.S.C. 2401(d))) must also occur during the period of contract performance.

(f) The term "practical application" means to manufacture in the case of a composition or product, to practice in the case of a process or method, or to operate in the case of a machine or system; and, in each case, under such conditions as to establish that the invention is be

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[1] See References in Text note below.

ing utilized and that its benefits are to the extent permitted by law or Government regulations available to the public on reasonable terms.

(g) The term "made" when used in relation to any invention means the conception or first actual reduction to practice of such invention.

(h) The term "small business firm" means a small business concern as defined at section 2 of Public Law 85-536 (15 U.S.C. 632) and implementing regulations of the Administrator of the Small Business Administration.

(i) The term "nonprofit organization" means universities and other institutions of higher education or an organization of the type described in section 501(c)(3) of the Internal Revenue Code of 1986 (26 U.S.C. 501(c)) and exempt from taxation under section 501(a) of the Internal Revenue Code (26 U.S.C. 501(a)) or any nonprofit scientific or educational organization qualified under a State nonprofit organization statute.

3. 35 U.S.C. 202 provides:

Disposition of rights

(a) Each nonprofit organization or small business firm may, within a reasonable time after disclosure as required by paragraph (c)(1) of this section, elect to retain title to any subject invention: *Provided, however,* That a funding agreement may provide otherwise (i) when the contractor is not located in the United States or does not have a place of business located in the United States or is subject to the control of a foreign government, (ii) in exceptional circumstances when it is determined by the agency that restriction or elimination of

the right to retain title to any subject invention will better promote the policy and objectives of this chapter (iii) when it is determined by a Government authority which is authorized by statute or Executive order to conduct foreign intelligence or counter-intelligence activities that the restriction or elimination of the right to retain title to any subject invention is necessary to protect the security of such activities or, (iv) when the funding agreement includes the operation of a Government-owned, contractor-operated facility of the Department of Energy primarily dedicated to that Department's naval nuclear propulsion or weapons related programs and all funding agreement limitations under this subparagraph on the contractor's right to elect title to a subject invention are limited to inventions occurring under the above two programs of the Department of Energy. The rights of the nonprofit organization or small business firm shall be subject to the provisions of paragraph (c) of this section and the other provisions of this chapter.

(b)(1) The rights of the Government under subsection (a) shall not be exercised by a Federal agency unless it first determines that at least one of the conditions identified in clauses (i) through (iv) of subsection (a) exists. Except in the case of subsection (a)(iii), the agency shall file with the Secretary of Commerce, within thirty days after the award of the applicable funding agreement, a copy of such determination. In the case of a determination under subsection (a)(ii), the statement shall include an analysis justifying the determination. In the case of determinations applicable to funding agreements with small business firms, copies shall also be sent to the Chief Counsel for Advocacy of the Small Business Administration. If the Secretary of Commerce

believes that any individual determination or pattern of determinations is contrary to the policies and objectives of this chapter or otherwise not in conformance with this chapter, the Secretary shall so advise the head of the agency concerned and the Administrator of the Office of Federal Procurement Policy, and recommend corrective actions.

(2) Whenever the Administrator of the Office of Federal Procurement Policy has determined that one or more Federal agencies are utilizing the authority of clause (i) or (ii) of subsection (a) of this section in a manner that is contrary to the policies and objectives of this chapter, the Administrator is authorized to issue regulations describing classes of situations in which agencies may not exercise the authorities of those clauses.

(3) At least once every 5 years, the Comptroller General shall transmit a report to the Committees on the Judiciary of the Senate and House of Representatives on the manner in which this chapter is being implemented by the agencies and on such other aspects of Government patent policies and practices with respect to federally funded inventions as the Comptroller General believes appropriate.

(4) If the contractor believes that a determination is contrary to the policies and objectives of this chapter or constitutes an abuse of discretion by the agency, the determination shall be subject to the[1] section 203(b).

(c) Each funding agreement with a small business firm or nonprofit organization shall contain appropriate provisions to effectuate the following:

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[1] So in original. The word "the" probably should not appear.

(1) That the contractor disclose each subject invention to the Federal agency within a reasonable time after it becomes known to contractor personnel responsible for the administration of patent matters, and that the Federal Government may receive title to any subject invention not disclosed to it within such time.

(2) That the contractor make a written election within two years after disclosure to the Federal agency (or such additional time as may be approved by the Federal agency) whether the contractor will retain title to a subject invention: *Provided*, That in any case where publication, on sale, or public use, has initiated the one year statutory period in which valid patent protection can still be obtained in the United States, the period for election may be shortened by the Federal agency to a date that is not more than sixty days prior to the end of the statutory period: *And provided further*, That the Federal Government may receive title to any subject invention in which the contractor does not elect to retain rights or fails to elect rights within such times.

(3) That a contractor electing rights in a subject invention agrees to file a patent application prior to any statutory bar date that may occur under this title due to publication, on sale, or public use, and shall thereafter file corresponding patent applications in other countries in which it wishes to retain title within reasonable times, and that the Federal Government may receive title to any subject inventions in the United States or other countries in which the contractor has not filed patent applications on the subject invention within such times.

(4) With respect to any invention in which the contractor elects rights, the Federal agency shall have a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world: *Provided*, That the funding agreement may provide for such additional rights, including the right to assign or have assigned foreign patent rights in the subject invention, as are determined by the agency as necessary for meeting the obligations of the United States under any treaty, international agreement, arrangement of cooperation, memorandum of understanding, or similar arrangement, including military agreement relating to weapons development and production.

(5) The right of the Federal agency to require periodic reporting on the utilization or efforts at obtaining utilization that are being made by the contractor or his licensees or assignees: *Provided*, That any such information as well as any information on utilization or efforts at obtaining utilization obtained as part of a proceeding under section 203 of this chapter shall be treated by the Federal agency as commercial and financial information obtained from a person and privileged and confidential and not subject to disclosure under section 552 of title 5.

(6) An obligation on the part of the contractor, in the event a United States patent application is filed by or on its behalf or by any assignee of the contractor, to include within the specification of such application and any patent issuing thereon, a statement specifying that the invention was made with Govern-

ment support and that the Government has certain rights in the invention.

(7) In the case of a nonprofit organization, (A) a prohibition upon the assignment of rights to a subject invention in the United States without the approval of the Federal agency, except where such assignment is made to an organization which has as one of its primary functions the management of inventions (provided that such assignee shall be subject to the same provisions as the contractor); (B) a requirement that the contractor share royalties with the inventor; (C) except with respect to a funding agreement for the operation of a Government-owned-contractor-operated facility, a requirement that the balance of any royalties or income earned by the contractor with respect to subject inventions, after payment of expenses (including payments to inventors) incidental to the administration of subject inventions, be utilized for the support of scientific research or education; (D) a requirement that, except where it proves infeasible after a reasonable inquiry, in the licensing of subject inventions shall be given to small business firms; and (E) with respect to a funding agreement for the operation of a Government-owned-contractor-operated facility, requirements (i) that after payment of patenting costs, licensing costs, payments to inventors, and other expenses incidental to the administration of subject inventions, 100 percent of the balance of any royalties or income earned and retained by the contractor during any fiscal year up to an amount equal to 5 percent of the annual budget of the facility, shall be used by the contractor for scientific research, development, and education con-

sistent with the research and development mission and objectives of the facility, including activities that increase the licensing potential of other inventions of the facility; provided that if said balance exceeds 5 percent of the annual budget of the facility, that 75 percent of such excess shall be paid to the Treasury of the United States and the remaining 25 percent shall be used for the same purposes as described above in this clause (D); and (ii) that, to the extent it provides the most effective technology transfer, the licensing of subject inventions shall be administered by contractor employees on location at the facility.

(8) The requirements of sections 203 and 204 of this chapter.

(d) If a contractor does not elect to retain title to a subject invention in cases subject to this section, the Federal agency may consider and after consultation with the contractor grant requests for retention of rights by the inventor subject to the provisions of this Act and regulations promulgated hereunder.

(e) In any case when a Federal employee is a coinventor of any invention made with a nonprofit organization, a small business firm, or a non-Federal inventor, the Federal agency employing such coinventor may, for the purpose of consolidating rights in the invention and if it finds that it would expedite the development of the invention—

(1) license or assign whatever rights it may acquire in the subject invention to the nonprofit organization, small business firm, or non-Federal inventor in accordance with the provisions of this chapter; or

(2) acquire any rights in the subject invention from the nonprofit organization, small business firm, or non-Federal inventor, but only to the extent the party from whom the rights are acquired voluntarily enters into the transaction and no other transaction under this chapter is conditioned on such acquisition.

(f)(1) No funding agreement with a small business firm or nonprofit organization shall contain a provision allowing a Federal agency to require the licensing to third parties of inventions owned by the contractor that are not subject inventions unless such provision has been approved by the head of the agency and a written justification has been signed by the head of the agency. Any such provision shall clearly state whether the licensing may be required in connection with the practice of a subject invention, a specifically identified work object, or both. The head of the agency may not delegate the authority to approve provisions or sign justifications required by this paragraph.

(2) A Federal agency shall not require the licensing of third parties under any such provision unless the head of the agency determines that the use of the invention by others is necessary for the practice of a subject invention or for the use of a work object of the funding agreement and that such action is necessary to achieve the practical application of the subject invention or work object. Any such determination shall be on the record after an opportunity for an agency hearing. Any action commenced for judicial review of such determination shall be brought within sixty days after notification of such determination.

4. 35 U.S.C. 203 provides:

March-in rights

(a) With respect to any subject invention in which a small business firm or nonprofit organization has acquired title under this chapter, the Federal agency under whose funding agreement the subject invention was made shall have the right, in accordance with such procedures as are provided in regulations promulgated hereunder to require the contractor, an assignee or exclusive licensee of a subject invention to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable under the circumstances, and if the contractor, assignee, or exclusive licensee refuses such request, to grant such a license itself, if the Federal agency determines that such—

(1) action is necessary because the contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject invention in such field of use;

(2) action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees;

(3) action is necessary to meet requirements for public use specified by Federal regulations and such requirements are not reasonably satisfied by the contractor, assignee, or licensees; or

(4) action is necessary because the agreement required by section 204 has not been obtained or waived or because a licensee of the exclusive right to

use or sell any subject invention in the United States is in breach of its agreement obtained pursuant to section 204.

(b) A determination pursuant to this section or section 202(b)(4) shall not be subject to the Contract Disputes Act (41 U.S.C. § 601 et seq.). An administrative appeals procedure shall be established by regulations promulgated in accordance with section 206. Additionally, any contractor, inventor, assignee, or exclusive licensee adversely affected by a determination under this section may, at any time within sixty days after the determination is issued, file a petition in the United States Court of Federal Claims, which shall have jurisdiction to determine the appeal on the record and to affirm, reverse, remand or modify, as appropriate, the determination of the Federal agency. In cases described in paragraphs (1) and (3) of subsection (a), the agency's determination shall be held in abeyance pending the exhaustion of appeals or petitions filed under the preceding sentence.

b. 35 U.S.C. 204 provides:

Preference for United States industry

Notwithstanding any other provision of this chapter, no small business firm or nonprofit organization which receives title to any subject invention and no assignee of any such small business firm or nonprofit organization shall grant to any person the exclusive right to use or sell any subject invention in the United States unless such person agrees that any products embodying the subject invention or produced through the use of the subject invention will be manufactured substantially in

the United States. However, in individual cases, the requirement for such an agreement may be waived by the Federal agency under whose funding agreement the invention was made upon a showing by the small business firm, nonprofit organization, or assignee that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible.

6. 35 U.S.C. 205 provides:

Confidentiality

Federal agencies are authorized to withhold from disclosure to the public information disclosing any invention in which the Federal Government owns or may own a right, title, or interest (including a nonexclusive license) for a reasonable time in order for a patent application to be filed. Furthermore, Federal agencies shall not be required to release copies of any document which is part of an application for patent filed with the United States Patent and Trademark Office or with any foreign patent office.

7. 35 U.S.C. 206 provides:

Uniform clauses and regulations

The Secretary of Commerce may issue regulations which may be made applicable to Federal agencies implementing the provisions of sections 202 through 204 of this chapter and shall establish standard funding agree-

ment provisions required under this chapter. The regulations and the standard funding agreement shall be subject to public comment before their issuance.

8. 35 U.S.C. 207 provides:

Domestic and foreign protection of federally owned inventions

(a) Each Federal agency is authorized to—

(1) apply for, obtain, and maintain patents or other forms of protection in the United States and in foreign countries on inventions in which the Federal Government owns a right, title, or interest;

(2) grant nonexclusive, exclusive, or partially exclusive licenses under federally owned inventions, royalty-free or for royalties or other consideration, and on such terms and conditions, including the grant to the licensee of the right of enforcement pursuant to the provisions of chapter 29 of this title as determined appropriate in the public interest;

(3) undertake all other suitable and necessary steps to protect and administer rights to federally owned inventions on behalf of the Federal Government either directly or through contract, including acquiring rights for and administering royalties to the Federal Government in any invention, but only to the extent the party from whom the rights are acquired voluntarily enters into the transaction, to facilitate the licensing of a federally owned invention; and

(4) transfer custody and administration, in whole or in part, to another Federal agency, of the right, title, or interest in any federally owned invention.

(b) For the purpose of assuring the effective management of Government-owned inventions, the Secretary of Commerce is authorized to—

(1) assist Federal agency efforts to promote the licensing and utilization of Government-owned inventions;

(2) assist Federal agencies in seeking protection and maintaining inventions in foreign countries, including the payment of fees and costs connected therewith; and

(3) consult with and advise Federal agencies as to areas of science and technology research and development with potential for commercial utilization.

9. 35 U.S.C. 208 provides:

Regulations governing Federal licensing

The Secretary of Commerce is authorized to promulgate regulations specifying the terms and conditions upon which any federally owned invention, other than inventions owned by the Tennessee Valley Authority, may be licensed on a nonexclusive, partially exclusive, or exclusive basis.

10. 35 U.S.C. 209 provides:

Licensing federally owned inventions

(a) AUTHORITY.—A Federal agency may grant an exclusive or partially exclusive license on a federally owned invention under section 207(a)(2) only if–

(1) granting the license is a reasonable and necessary incentive to—

(A) call forth the investment capital and expenditures needed to bring the invention to practical application; or

(B) otherwise promote the invention's utilization by the public;

(2) the Federal agency finds that the public will be served by the granting of the license, as indicated by the applicant's intentions, plans, and ability to bring the invention to practical application or otherwise promote the invention's utilization by the public, and that the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application, as proposed by the applicant, or otherwise to promote the invention's utilization by the public;

(3) the applicant makes a commitment to achieve practical application of the invention within a reasonable time, which time may be extended by the agency upon the applicant's request and the applicant's demonstration that the refusal of such extension would be unreasonable;

(4) granting the license will not tend to substantially lessen competition or create or maintain a violation of the Federal antitrust laws; and

(5) in the case of an invention covered by a foreign patent application or patent, the interests of the Federal Government or United States industry in foreign commerce will be enhanced.

(b) MANUFACTURE IN UNITED STATES.—A Federal agency shall normally grant a license under section 207(a)(2) to use or sell any federally owned invention in the United States only to a licensee who agrees that any products embodying the invention or produced through the use of the invention will be manufactured substantially in the United States.

(c) SMALL BUSINESS.—First preference for the granting of any exclusive or partially exclusive licenses under section 207(a)(2) shall be given to small business firms having equal or greater likelihood as other applicants to bring the invention to practical application within a reasonable time.

(d) TERMS AND CONDITIONS.—Any licenses granted under section 207(a)(2) shall contain such terms and conditions as the granting agency considers appropriate, and shall include provisions—

(1) retaining a nontransferrable, irrevocable, paid-up license for any Federal agency to practice the invention or have the invention practiced throughout the world by or on behalf of the Government of the United States;

(2) requiring periodic reporting on utilization of the invention, and utilization efforts, by the licensee,

but only to the extent necessary to enable the Federal agency to determine whether the terms of the license are being complied with, except that any such report shall be treated by the Federal agency as commercial and financial information obtained from a person and privileged and confidential and not subject to disclosure under section 552 of title 5; and

(3) empowering the Federal agency to terminate the license in whole or in part if the agency determines that

(A) the licensee is not executing its commitment to achieve practical application of the invention, including commitments contained in any plan submitted in support of its request for a license, and the licensee cannot otherwise demonstrate to the satisfaction of the Federal agency that it has taken, or can be expected to take within a reasonable time, effective steps to achieve practical application of the invention;

(B) the licensee is in breach of an agreement described in subsection (b);

(C) termination is necessary to meet requirements for public use specified by Federal regulations issued after the date of the license, and such requirements are not reasonably satisfied by the licensee; or

(D) the licensee has been found by a court of competent jurisdiction to have violated the Federal antitrust laws in connection with its performance under the license agreement.

(e) PUBLIC NOTICE.—No exclusive or partially exclusive license may be granted under section 207(a)(2) unless public notice of the intention to grant an exclusive or partially exclusive license on a federally owned invention has been provided in an appropriate manner at least 15 days before the license is granted, and the Federal agency has considered all comments received before the end of the comment period in response to that public notice. This subsection shall not apply to the licensing of inventions made under a cooperative research and development agreement entered into under section 12 of the Stevenson-Wydler Technology Innovation Act of 1980 (15 U.S.C. 3710a).

(f) PLAN.—No Federal agency shall grant any license under a patent or patent application on a federally owned invention unless the person requesting the license has supplied the agency with a plan for development or marketing of the invention, except that any such plan shall be treated by the Federal agency as commercial and financial information obtained from a person and privileged and confidential and not subject to disclosure under section 552 of title 5.

11. 35 U.S.C. 210 provides:

Precedence of chapter

(a) This chapter shall take precedence over any other Act which would require a disposition of rights in subject inventions of small business firms or nonprofit organizations contractors in a manner that is inconsistent with this chapter, including but not necessarily limited to the following:

(1) section 10(a) of the Act of June 29, 1935, as added by title I of the Act of August 14, 1946 (7 U.S.C. 427i(a); 60 Stat. 1085);

(2) section 205(a) of the Act of August 14, 1946 (7 U.S.C. 1624(a); 60 Stat. 1090);

(3) section 501(c) of the Federal Mine Safety and Health Act of 1977 (30 U.S.C. 951(c); 83 Stat. 742);

(4) section 30168(e) of title 49;

(5) section 12 of the National Science Foundation Act of 1950 (42 U.S.C. 1871(a);[1] 82 Stat. 360);

(6) section 152 of the Atomic Energy Act of 1954 (42 U.S.C. 2182; 68 Stat. 943);

(7) section 305 of the National Aeronautics and Space Act of 1958 (42 U.S.C. 2457);

(8) section 6 of the Coal Research and Development Act of 1960 (30 U.S.C. 666; 74 Stat. 337);

(9) section 4 of the Helium Act Amendments of 1960 (50 U.S.C. 167b; 74 Stat. 920);

(10) section 32 of the Arms Control and Disarmament Act of 1961 (22 U.S.C. 2572; 75 Stat. 634);

(11) section 9 of the Federal Nonnuclear Energy Research and Development Act of 1974 (42 U.S.C. 5908; 88 Stat. 1878);

(12) section 5(d) of the Consumer Product Safety Act (15 U.S.C. 2054(d); 86 Stat. 1211);

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[1] See References in Text note below.

(13) section 3 of the Act of April 5, 1944 (30 U.S.C. 323; 58 Stat. 191);[1]

(14) section 8001(c)(3) of the Solid Waste Disposal Act (42 U.S.C. 6981(c); 90 Stat. 2829);

(15) section 219 of the Foreign Assistance Act of 1961 (22 U.S.C. 2179; 83 Stat. 806);

(16) section 427(b) of the Federal Mine Health and Safety Act of 1977 (30 U.S.C. 937(b); 86 Stat. 155);

(17) section 306(d) of the Surface Mining and Reclamation Act of 1977 (30 U.S.C. 1226(d); 91 Stat. 455);[1]

(18) section 21(d) of the Federal Fire Prevention and Control Act of 1974 (15 U.S.C. 2218(d); 88 Stat. 1548);

(19) section 6(b) of the Solar Photovoltaic Energy Research Development and Demonstration Act of 1978 (42 U.S.C. 5585(b); 92 Stat. 2516);

(20) section 12 of the Native Latex Commercialization and Economic Development Act of 1978 (7 U.S.C. 178j, 92 Stat. 2533); and

(21) section 408 of the Water Resources and Development Act of 1978 (42 U.S.C. 7879; 92 Stat. 1360).

The Act creating this chapter shall be construed to take precedence over any future Act unless that Act specifically cites this Act and provides that it shall take precedence over this Act.

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[1] See References in text note below.

(b) Nothing in this chapter is intended to alter the effect of the laws cited in paragraph (a) of this section or any other laws with respect to the disposition of rights in inventions made in the performance of funding agreements with persons other than nonprofit organizations or small business firms.

(c) Nothing in this chapter is intended to limit the authority of agencies to agree to the disposition of rights in inventions made in the performance of work under funding agreements with persons other than nonprofit organizations or small business firms in accordance with the Statement of Government Patent Policy issued on February 18, 1983, agency regulations, or other applicable regulations or to otherwise limit the authority of agencies to allow such persons to retain ownership of inventions except that all funding agreements, including those with other than small business firms and nonprofit organizations, shall include the requirements established in section 202(c)(4) and section 203 of this title. Any disposition of rights in inventions made in accordance with the Statement or implementing regulations, including any disposition occurring before enactment of this section, are hereby authorized.

(d) Nothing in this chapter shall be construed to require the disclosure of intelligence sources or methods or to otherwise affect the authority granted to the Director of Central Intelligence by statute or Executive order for the protection of intelligence sources or methods.

(e) The provisions of the Stevenson-Wydler Technology Innovation Act of 1980 shall take precedence over the provisions of this chapter to the extent that they permit or require a disposition of rights in subject inventions which is inconsistent with this chapter.

12. 37 C.F.R. 401.9 provides:

Retention of rights by contractor employee inventor.

Agencies which allow an employee/inventor of the contractor to retain rights to a subject invention made under a funding agreement with a small business firm or nonprofit organization contractor, as authorized by 35 U.S.C. 202(d), will impose upon the inventor at least those conditions that would apply to a small business firm contractor under paragraphs (d)(1) and (3); (f)(4); (h); (i); and (j) of the clause at § 401.14(a).

AMICUS CURIAE BRIEF

No. 09-1159

IN THE

Supreme Court of the United States

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., *et al.*,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF AMERICAN ASSOCIATION OF UNIVERSITY PROFESSORS, IEEE-USA, AND IP ADVOCATE AS *AMICI CURIAE* IN SUPPORT OF AFFIRMANCE

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INTEREST OF *AMICI CURIAE* [1]

Founded in 1915, the American Association of University Professors (AAUP) is a non-profit organization of approximately 47,000 faculty, librarians, graduate students, and academic professionals. Its purpose is to advance academic freedom and shared university governance, to define fundamental professional values and standards for higher education, and to ensure higher education's contribution to the common good. As a guardian of academic freedom and an advocate for faculty rights, one of the AAUP's principal tasks is to formulate national standards, often in conjunction with other higher education organizations, for the protection of academic freedom and other important aspects of university life. These standards serve as models for institutional policy on matters like academic freedom, due process, research, and teaching. *E.g.*, *1915 Declaration of Principles on Academic Freedom & Academic Tenure* and *1940 Statement of Principles on Academic Freedom & Tenure, in* AAUP POLICY DOCUMENTS & REPORTS 3-11, 291-301 (10th ed., 2006).

Because the AAUP's policies have been recognized by this Court and are widely respected and followed in American colleges and universities, the AAUP is uniquely positioned to assist this Court in developing the law in a manner that respects aca-

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[1] No counsel for a party authored this brief in whole or in part, nor made a monetary contribution intended to fund the preparation or submission of the brief. No one other than *Amici* their members or counsel made a monetary contribution to the preparation or submission of this brief. Pursuant to this Court's Rule 37.3(a), letters of consent were filed by the parties.

demic practice in higher education for the treatment of faculty intellectual property. *See, e.g., Board of Regents v. Roth*, 408 U.S. 564, 579 n.17 (1972); *Tilton v. Richardson*, 403 U.S. 672, 681-82 (1971). In cases that implicate AAUP policies, or otherwise raise legal issues important to higher education or faculty members, the AAUP frequently submits *amicus* briefs to the Court. *See, e.g., Garcetti v. Ceballos*, 547 U.S. 410 (2006); *Grutter v. Bollinger*, 539 U.S. 306 (2003); *Regents of Univ. of Michigan v. Ewing*, 474 U.S. 214 (1985); and *Keyishian v. Bd. of Regents*, 385 U.S. 589 (1967).

Faculty and academic professionals at institutions of higher education serve a critical societal function, vesting them with both enhanced rights and greater responsibilities to the colleges and universities where they engage in scholarship and research, as well as to their students and to society as a whole. As stated by the AAUP's *1915 Declaration of Principles on Academic Freedom and Academic Tenure*, the profession's first statement on academic freedom and tenure, "[i]f education is the cornerstone of the structure of society and if progress in scientific knowledge is essential to civilization, few things can be more important than to enhance the dignity of the scholar's profession.... The responsibility of the university teacher is primarily to the public itself, and to the judgment of his own profession." *1915 Declaration*, at 294-295. Thus, faculty researchers and inventors are, and always have been, more than mere employees to their institutions.

By participating as an *amicus* in this case, the AAUP seeks to educate the Court about the ownership interests of faculty inventors and the impor-

tance of those interests to higher education and to society as a whole.

IEEE-USA is an organizational unit of The Institute of Electrical and Electronics Engineers, Inc., a New York-based not-for-profit and the world's leading educational and scientific association for the advancement of technology. IEEE-USA supports the nation's prosperity and competitiveness by fostering technological innovation for the benefit of all, including U.S. IEEE members—more than 210,000 engineers, scientists, and allied professionals. As part of its mission, IEEE-USA seeks to ensure that U.S. patent and copyright law promotes the progress of science and the useful arts consistent with the principles set forth by our nation's founders. IEEE's U.S. members serve on the "front line" of our copyright and patent system. Its membership includes inventors, software authors, and others who create and use cutting-edge technology, who research and publish professional articles and journals, and who develop published standards that form the bases for widely-adopted and critical technologies. They are academics, entrepreneurs, and employees of firms that acquire, license, and market patented works. While the outcome of this appeal may well affect all members, the ruling will directly affect the nearly 30% of IEEE-USA members in academia.

Recognizing that the promotion of progress requires a delicate balancing of these groups' interests, IEEE-USA consistently speaks for that balance. When a decision threatens to disrupt the nation's intellectual property system, IEEE-USA respectfully believes it has the experience and perspective to aid this Court as it interprets the law to achieve the con-

stitutional directive of promoting progress. It has done so previously as an *amicus* in *Bilski v. Kappos*, 130 S. Ct. 3218 (2010), *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002), and *MGM Studios, Inc. v. Grokster, Ltd.*, 545 U.S. 913 (2005), suggesting balanced approaches consistent with those adopted by the Court. This case affects two groups of IEEE-USA members. First, members who invent must have the ability to contract, assign for consideration, or license their inventions to entities that can assemble the capital and business resources to bring the inventions to market in useable form. Second, members who own or are employed by companies that acquire inventions based on federally-funded research must have assurance they receive quiet title. Absent that, companies will lack the confidence to invest and build businesses based on these inventions. The fear of late-arising Bayh-Dole claims for revocation of intellectual property title necessary to build those businesses will disrupt their formation and harm the economy.

IEEE-USA recognizes the pivotal role that universities and other federally-funded research institutions play in achieving the goals enunciated above and has generally supported contractual procedures that properly transfer certain original inventors' rights to universities for inventions developed at the university during, and in the course of, federally-funded research. As the *Position Statement On University Intellectual Property Guidelines* adopted by the IEEE-USA on November 19, 2010 states, however, universities should "obtain signed intellectual property agreements from all applicable faculty, staff and students, indicating that they have been

informed of the university's intellectual property policies, and agree to abide by them." The Statement elaborates that, "[T]he university should also inform faculty, staff and students who will be working on a grant or contract whenever that grant or contract contains terms that affect the ownership of intellectual property." This case arose in part because such proper procedures were not followed and necessary assignment agreements were not secured. Affirming the decision below, *Amici* assert, would respect the bargained-for protections in place for academic inventors, while reversing it would frustrate this established, successful structure for managing intellectual property in universities.

IP Advocate is a philanthropic organization dedicated to assisting academic researchers in comprehending and traversing the complex interplay of policy, law, and procedure throughout the creation, development, technology transfer, and commercialization of their intellectual property. The founder of IP Advocate, Dr. Renee Kaswan, spent eighteen years as a research professor at the University of Georgia, where she invented and patented the Chronic Dry Eye drugs Optimmune® and Restasis®. The university awarded her its Creative Research Medal in 1992, and recognized Dr. Kaswan as its "Inventor of the Year" in 1998. Her inventions have generated over $2 billion in sales. The University of Virginia Patent Foundation ranked Restasis® amongst the "University Inventions that Changed the World."

The AAUP, IEEE-USA, and IP Advocate submit this brief to refute the notion fostered by, *e.g.*, the Association of University Technology Managers (AUTM) and the Association of American Universi-

ties (AAU), that the American research university community as a monolithic whole wants the decision of the U.S. Court of Appeals for the Federal Circuit reversed. A critical mass of the most indispensable university constituency affected—professors and others whose scholarly work generates the inventions at stake—in fact opposes judicially rewriting the Bayh-Dole Act to divest faculty and similarly-situated inventors of the right to initial ownership of their inventions.

SUMMARY OF THE ARGUMENT

This case commenced as a fact-intensive dispute over the role of a single scientist in an inventive collaboration spanning several years that utilized the resources of both private enterprise and a top research university—with, *allegedly*,[2] a dose of federal funding injected at some point. Stanford researcher Dr. Holodniy learned about the Nobel Prize-winning PCR technique from its creator, Cetus. Back in a Stanford laboratory, Holodniy and others tested the PCR-based assay for HIV quantitation that resulted from his work at Cetus, which Stanford filed patent applications to cover. Meanwhile, Roche acquired Cetus's PCR assets, and commercialized an HIV therapy effectiveness test based on this technology. No one questions the benefits of this development.

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[2] As discussed in Respondents' brief, *Amici* see no evidence in the record or Petitioner's brief that explains exactly how two grant agreements Stanford apparently cannot produce copies of ever covered any part of Dr. Holodniy's work on the claimed inventions in the first place.

While both sides praise the Bayh-Dole Act and laud its impact during its thirty years in force, this appeal has turned into an epic debate over whether one group or another reaping the rewards misunderstood all along how the Act functions. Now Petitioner and Respondents both claim that adopting the other side's construction of Bayh-Dole would jeopardize their widely-celebrated, collective success. Respondents' reading of the Act, however, best comports with the record, including evidence of the historical behavior of institutions like Petitioner.

Amici contend that the correct interpretation of Bayh-Dole starts with the choice of the Constitution and Patent Act to grant patents to individuals, the longstanding recognition by universities that faculty initially own their inventions and that written assignments are required to transfer title, and the language of the Bayh-Dole Act itself that simply allows contractors to "retain" what title they obtained through such assignments. The Act should not be read to upset this balance after-the-fact and vest title to federally-funded inventions in contractors.

ARGUMENT

I. THE BAYH-DOLE ACT DOES NOT ALTER THE EXISTING RELATIONSHIPS BETWEEN UNIVERSITIES AND FACULTY.

Without repeating fully their well-presented arguments, the AAUP, IEEE-USA, and IP Advocate join in the view taken by Parts I-V of the neutral *amicus* brief filed by the American Intellectual Property Law Association (AIPLA), and Part I of Respondents' brief. As each similarly sets forth, the Consti-

tution and the Patent Act provide to inventors the initial ownership rights in patents. Inventors can then assign or transfer their rights in writing, under 35 U.S.C. § 261.

Nothing in the Bayh-Dole Act's language or legislative history suggests the automatic taking of this title from inventors, as Petitioner and its supporters imagine, to vest it by operation of law in a contractor under a federal funding agreement. Unable to point to any such literal language, Petitioner would rewrite the Act's provision that a contractor may "elect to *retain* title" to assert instead that Bayh-Dole "Section 202(a) contains the critical right to *take* title ...." *Compare* 35 U.S.C. § 202(a) *with* Pet. Br. at 12 (emphases added). The wording of the Act quite simply allows a contractor to *retain* an interest in the title that it has the right to obtain or has obtained separately from inventors in its employ.

The *amicus* brief of the National Venture Capital Association (NVCA), though in support of Petitioner, aids in illuminating how the backdrop and legislative history of the Bayh-Dole Act instead support Respondents' interpretation. NVCA points out that "[i]t was evident by 1980 that universities had been successful in licensing their portfolios of patents arising out of private funding to startups and other companies." NVCA Br. at 9; *see also* S. Rep. No. 96-480, at 2 (praising the ability of universities prior to Bayh-Dole to license one-third of the patents they held, in contrast to the government's ability to license less than four percent of the patents it had taken title to). In other words, prior to passage of Bayh-Dole, and without the aid of any law that vested title in universities, they were able to con-

tract successfully with inventors for assignments of patents that the universities could then license out.

NVCA rightly cites this "proven track record" as the grounds for "Congress's judgment [] that non-profits would be effective custodians of federal inventions, much as they had been with private institutions." NVCA Br. at 9-10; *see* H.R. Rep. No., 96-1307, pt. 1, at 3. If the goal of Bayh-Dole was to put universities on the same footing with respect to federally-funded research as private entities who acquire title from their employees by contract, as NVCA states, that cannot justify taking title by legal fiat from faculty inventors and transferring that title to the colleges and universities where they engaged in scholarly research. These institutions can and do regularly contract with their employee-inventors without any special federal statute.

In a 1978 press release, Senator Dole, co-namesake of the Act, stated his concern about the government's inability to efficiently commercialize federal funded inventions for the benefit of society when he criticized the Department of Health, Education and Welfare (HEW) for "suppressing critical lifesaving drugs and medical devices developed under support from the National Institutes of Health." Press Release, *News from U.S. Sen. Bob Dole, Dole Charges HEW Is Suppressing Lifesaving Medical Technology*, at 1 (August 4, 1978), *available at* http://bayhdolecetral.com/dolePDF/DoleChargesHEWPressRelease1978.pdf. He wrote, "HEW's present position of denying *to inventors* and their universities ownership rights ... precludes the possibility of those inventions ever reaching the public." *Id.* at 2 (emphasis added). Senator Dole's concern about the denial of

ownership rights "to inventors" funded by HEW cannot square with a reading of Bayh-Dole that instead automatically divests an even broader universe of nonprofit inventors of their rights. *See* Elizabeth P. Berman, *Why Did Universities Start Patenting?: Institution-building and the Road to the Bayh-Dole Act*, 38/6 Social Studies of Science 837 (Dec. 2008), *available at* http://sss.sagepub.com/content/38/6/835.full.pdf+html. "The third phase of institution building was the effort to change government patent policy that would ultimately result in Bayh-Dole. Starting in the early 1970s, a small group of federal administrators who believed that inventors in general should retain patent rights to government-funded research began working on several fronts to make that possible.").

Similarly, in a 2006 speech reflecting on the passage of the Act, former Senator Bayh recalled what the head of technology transfer at Purdue University said to him in 1978: "that the Government's policy that prohibited universities from owning these patents and leasing them to businesses killed the incentive necessary for innovative companies to fully develop these new ideas." Birch Bayh, U.S. Sen., *Bayh-Dole: Don't Turn Back the Clock (2006)*, *see* NVCA Br. at 9. In other words, the solution Bayh-Dole enshrined in law was to reallocate patent ownership rights as between the government and nonprofit entities including universities, not to alter the established and effective contractual relationships between those nonprofit higher education institutions and their faculty inventors.

As *amicus* AIPLA observes, the regulations implementing Bayh-Dole recognize the independent

need for a contractor to secure rights in subject inventions "by written agreement, [from] its employees ...." 37 C.F.R. § 401.14(a)(f)(2); *see* AIPLA Br. at 7-8. To protect the government's interests, this formalizes for federally-funded inventions in the hands of nonprofits what Congress praised universities for managing so efficiently in the realm of their privately-funded efforts. *See* AIPLA Br. at 10-11 (quoting 1947 AG Report 1, *at* 78, 88). Again, this contravenes the idea that Bayh-Dole already effectuated an automatic taking of title from inventors.

II. FACULTY MEMBERS ARE MORE THAN MERE EMPLOYEES "HIRED TO INVENT."

Higher education occupies a special place in this country. The academic work pursued at colleges and universities in the United States has long been recognized as central to our democracy, and conducted in support of the common good. As the joint *1940 Statement of Principles of Academic Freedom and Tenure*, coauthored by the AAUP and the Association of American Colleges (now the Association of American Colleges and Universities), eloquently states, "[t]he common good depends upon the free search for truth and its free exposition.... Freedom in research is fundamental to the advancement of truth." *1940 Statement* at 3.[3]

Federal courts have credited faculty and academic professionals as the keystones in this work.

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[3] The *1940 Joint Statement* codified the AAUP's *1915 Declaration* and is recognized as the profession's seminal statement; it has been endorsed by more than 240 disciplinary societies and educational organizations.

This Court encapsulated this notion in *Sweezy v. New Hampshire*, 354 U.S. 234, 250 (1957):

> The essentiality of freedom in the community of American universities is almost self-evident. No one should underestimate the vital role in a democracy that is played by those who guide and train our youth. To impose any strait jacket upon the intellectual leaders in our colleges and universities would imperil the future of our Nation.

The Court reaffirmed its commitment to academic freedom in *Keyishian v. Bd. of Regents*, 385 U.S. 589, 603 (1967), in which Justice Brennan, for a unanimous court finding faculty loyalty oaths unconstitutional, wrote that "[o]ur Nation is deeply committed to safeguarding academic freedom, which is of transcendent value to all of us.... That freedom is therefore a special concern."

The relationship between a faculty member and his or her college or university is, therefore, much more than merely that of an employee to his or her employer. As articulated in the AAUP's *1915 Declaration*, "[t]he [faculty] are the appointees, but not in any proper sense the employees of [the university trustees]. *1915 Declaration* at 295. This Court and other courts have acknowledged the unique relationship of faculty to their colleges and universities, often referring to the importance of protecting academic freedom in the context of academic speech or other faculty decision-making. *See, e.g., Grutter v. Bollinger*, 539 U.S. 306, 321 (2003) (citing academic freedom considerations as a reason for the Court to defer to faculty decision-making in the development

of state university admissions processes); *Regents of the University of Michigan v. Ewing*, 474 U.S. 214, 226 (1985) (citing academic freedom concerns in deferring to faculty decision-making about academic matters with respect to decision to drop student from special medical school program).

Thus it is particularly concerning to *Amici* that key arguments of Petitioner and the AAU, AUTM, *et al.*, urge extension of the purportedly-analogous "hired to invent" or "work made for hire" doctrines in ways that might diminish the rights of academic inventors under the Bayh-Dole Act. Petitioner looks to "general federal common law" as applied in a lone 1924 decision, *see* Petitioner's Br. at 57-58, which Respondents easily distinguish, *see* Respondents' Br. at 70-71. Unlike the normal role of academic researchers, Mr. Peck developed precisely the process and machinery his short-term employment contract engaged him to invent to solve an expressly-defined problem. *Standard Parts Co. v. Peck*, 264 U.S. 52, 59-60 (1924). Had Congress intended to extrapolate so profoundly from this narrow opinion, or to synchronize patent law with "work made for hire" in sections 101 and 201(b) of the Copyright Act, *see* 17 U.S.C. §§ 101, 201(b), one would expect to find some scintilla of evidence in the Bayh-Dole language or its legislative history. As the briefs supporting Petitioner reveal, no such evidence can be found.

The attempted analogy to the Copyright Act's work for hire doctrine fails for two additional reasons. As a basic matter, the Patent Act has absolutely no provision mirroring the Copyright Act's "work made for hire" approach. The Patent Act states that patent ownership is granted to inventors.

35 U.S.C. § 261. In addition, unlike Mr. Peck or others hired to develop specific inventions, faculty researchers and scholars have significant independent control over the areas in which they conduct research, as well as the content of their teaching. The work of faculty inventors, therefore, does not meet the traditional requirements of a work for hire.

Although the AAUP has not published a statement directly addressing ownership interests of faculty in inventive works, the *1999 Statement on Copyright* explains that the "prevailing academic practice [has been] to treat the faculty member as the copyright owner of works that are created independently and at the faculty member's own initiative for traditional academic purposes." AAUP POLICY DOCUMENTS & REPORTS, at 214.

This prevailing practice has been recognized by the federal courts. For example, as Judge Posner stated in *Hays v. Sony Corporation of America*, 847 F.2d 413, 416 (7th Cir. 1988):

> Although college and university teachers do academic writing as a part of their employment responsibilities and use their employer's paper, copier, secretarial staff, and (often) computer facilities in that writing, the universal assumption and practice was that (in the absence of an explicit agreement as to who had the right to copyright) the right to copyright such writing belonged to the teacher rather than to the college or university. There were good reasons for the assumption. A college or university does not

> supervise its faculty in the preparation of academic books and articles.[4]

Explicitly under the Patent Act, therefore, scholarly inventive work is owned by the faculty inventor and could not be deemed work-for-hire without violating the basic tenets of academic freedom—tenets that are fundamental to higher education and that ensure continued benefits to students, the community, and the public as a whole. Contrary to what Petitioner and AAU, AUTM, *et al.*, imply, faculty ownership of their inventive work accordingly is consistent with the purpose of the Bayh-Dole Act.

As Senator Dole wrote in mustering support for the Act, "Our economy is one which has always run on America's innovative genius." Press Release, Bob Dole, U.S. Sen., *'Public the Victim' for Lack of Limited Patent Right Policy, Dole Says* (May 16, 1979), *available at* http://bayhdolecentral.com/dolePDF/PatentPolicyPublicVictimPressRelease1979.pdf. That "fire of genius"[5] burns in the minds of individuals who work alone or collaborate to manifest it in tangible inventions, not abstractly in institutions that dictate to them what to create. Quite the opposite of what Petitioner implies, "faculty members engage in unique specializations in which the substantive con-

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[4] *See also Weinstein v. University of Illinois*, 811 F.2d 1091 (7th Cir. 1987) recognizing the practice that faculty owned their scholarly authored work unless the work falls into certain exceptions).

[5] *See* Abraham Lincoln, *Second Lecture on Discoveries & Inventions, in* 3 THE COLLECTED WORKS OF ABRAHAM LINCOLN 356, 363 (Roy P. Basler ed., Rutgers 1953) (Feb. 11, 1859).

tent may not be understood even by their first-line 'supervisor,' the department chairperson, who is a colleague." Martin Kenney & Donald Patten, *Reconsidering the Bayh-Dole Act and the Current University Invention Ownership Model*, *at* 1413 (2009). Indeed, "[m]any researchers choose a university career because of its relatively unstructured, unsupervised, and collegial environment."[6] *Id.* The suggestion to graft a "hired to invent" or "work made for hire" framework onto Bayh-Dole poses grave risks to the existing rights of faculty inventors, longstanding academic practice, and the public's interest in a flourishing culture of discovery and creation.

III. PETITIONER'S READING OF BAYH-DOLE CONTRAVENES THE HISTORICAL RECOGNITION THAT FACULTY INVENTORS OWN THEIR INVENTIONS.

Consistent with 37 C.F.R. § 401.14(a)(f)(2) and Attorney General Biddle's survey reported in 1947, *see* AIPLA Br. at 10, universities themselves routinely have operated pursuant to the understanding that they must secure assignments from inventors under the Bayh-Dole Act, exactly as they do for inventions beyond the scope of the Act. On this point, *Amici* commend to the Court Part VI of the AIPLA brief and Part I.B.3 of Respondents' brief.

Respondents point to Petitioner, along with the University of Wisconsin and Iowa State University—both signatories to the AAU, AUTM, *et al.*, brief—as

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[6] Respondents point out that Dr. Holodniy, far from being "hired to invent" anything specific, started out in clinical rotations at Stanford, before looking for possible research projects, which led to his work with Cetus. Respondents' Br. at 3.

examples of contractors whose written policies indisputably reflect an understanding that they bear the burden of securing assignments of ownership from inventors working on federally-funded research. *See* Respondents' Br. at 43. While *Amici* cannot locate the Intellectual Property Policy of each of the roughly seventy-five universities that joined the AAU, AUTM, *et al.*, brief, even a quick search reveals myriad examples, a few of which have been sampled below:

- **Brandeis University** —

> "The creator shall assign to the University all domestic and foreign rights to any such IP when requested to do so by the University, on forms provided for such purpose by the University."

Brandeis Intellectual Property Policy (Feb. 2004), *available at* http://www.brandeis.edu/otl/pdfs/ippolicy.pdf.

- **California Institute of Technology** —

> "I agree to assign, and hereby do assign, to the Institute all such inventions and copyrightable material...; and to execute all papers required."

California Institute of Technology Patent and Copyright Agreement (Dec. 30, 2003), *available at* https://www.ogc.caltech.edu/Forms/documents/patentagreement.

- **Cornell University**

> "Cornell University requires inventors to assign to the university or its designee all rights and titles of their inventions and related property rights that result from activity conducted in the course of an appointment with the university and/or using university resources, including those provided through an externally funded grant, contract, or other type of award or gift to the university."

Inventions and Related Property Rights, 1 Cornell University Policy Library (June 4, 2010), *available at* http://www.dfa.cornell.edu/dfa/cms/treasurer/policyoffice/policies/volumes/academic/upload/vol1_5.pdf.

Petitioner's argument that the decision on appeal throws "uncertainties" into the path of commercializing a "subject invention," *see* Petitioner's Br. at 46-47, dissipates when faced with the reality of these universities' own policies. The decision below hardly "ignores the statute's thirty-year period of consistent and successful application." *Id.* Rather, it acknowledges and respects that Bayh-Dole has worked as intended since passage by removing artificial distinctions imposed on federally-funded inventions.

Notably, even in this small sample, the California Institute of Technology policy, *supra*, demonstrates that universities can craft policies incorporating the language of present assignment relied on by the Federal Circuit, rather than obtaining "a mere prom-

ise to assign rights in the future." *Bd. of Trustees of the Leland Stanford Junior Univ. v. Roche Molecular Sys., Inc.*, 583 F.3d 832, 841 (Fed. Cir. 2009); *see also Imation Corp. v. Koninklijke Philips Elecs. N.V.*, 586 F.3d 980, 985-86 (Fed. Cir. 2009) (holding that "agrees to grant and does hereby grant" effectuated a present grant of rights in future inventions).

More importantly, these large sophisticated research universities have for thirty years engaged in the very process—acknowledging faculty ownership of inventions born from scholarly research and effectuating technology transfer of that ownership—that they now argue is unnecessary because Bayh-Dole vested title in them automatically for federally-funded inventions. Why maintain such a structured regime of securing assignments to inventions derived from federal funding for such a long period of time, if they already fully own them?

IV. APPLYING THE BAYH-DOLE ACT AS PETITIONER SEEKS WOULD DAMPEN PRIVATE ENTITIES' WILLINGNESS TO WORK WITH NONPROFIT RESEARCHERS.

Briefs for both sides opine on which outcome would chill collaboration between nonprofits and private enterprise, and stifle the ability to bring inventions covered by the Bayh-Dole Act to market. It is difficult to prove that reversing the Federal Circuit would destroy the willingness of businesses to welcome university researchers into their facilities. Yet *Amici* nevertheless agree with Part I.E.2 of Respondents' brief that a chilling effect more logically will spring from the fear that a single co-inventor associated with federal funds could deprive a private

business of contracted-for rights through newfound Bayh-Dole vesting.

Contrary to the briefs of Petitioner and its supporters, the need to monitor the outside activity of faculty that could trigger conflicts of interest raises no novel concerns. The AAUP publishes a statement of principles dating to 1965, in conjunction with the American Council on Education and the Federal Council of Science and Technology, which sets forth, under "University Responsibilities," that "[e]ach university participating in government-sponsored research should make known to the sponsoring government agencies ... [the university's] procedures that enable it to be aware of the outside professional work of staff members participating in government-sponsored research, if such outside work relates in any way to the government-sponsored research." *On Preventing Conflicts of Interest in Government-Sponsored Research at Universities* (1965), *in* AAUP POLICY DOCUMENTS & REPORTS at 184.

The AAUP has long emphasized both that faculty collaboration with industry is mutually beneficial, and that it presents the dangers that matured here:

> Consulting relationships between university staff members and industry serve the interests of research and education in the university. Likewise, the transfer of technical knowledge and skill from the university to industry contributes to technological advance. Such relationships are desirable, but certain potential hazards should be recognized.

Id. at 182. In this case, though, Cetus appears to have done everything normally assumed possible to

protect its rights, when it agreed to teach its Nobel Prize-winning PCR technique to Dr. Holodniy. Yet, if the Court adopts Petitioner's construction of the Bayh-Dole Act, Cetus will find its efforts undone by the bare assertion that two unproduced NIH grants connected in some unsubstantiated way with Holodniy's work at Stanford funded some still-undelineated portion of the overall project. That result, *Amici* contend, would chill future collaboration and commercialization.

CONCLUSION

For the foregoing reasons, the AAUP, IEEE-USA, and IP Advocate ask that this Court affirm the decision of the U.S. Court of Appeals for the Federal Circuit. The Court should decline Petitioner's invitation to turn the Bayh-Dole Act retroactively into a vesting statute, and thereby deprive a broad class of nonprofit researchers of their historical rights in the fruits of their inventive endeavors.

Respectfully submitted,

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BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Ninth Circuit

BRIEF OF AMICUS CURIAE, AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION IN SUPPORT OF NEITHER PARTY

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STATEMENT OF INTEREST[1]

The American Intellectual Property Law Association ("AIPLA") is a national bar association of approximately 16,000 members engaged in private and corporate practice, in government service, and in the academic community. AIPLA represents a wide and diverse spectrum of individuals, companies, and institutions involved directly and indirectly in the practice of patent, trademark, copyright, and unfair competition law, as well as other fields of law affecting intellectual property. AIPLA members represent both owners and users of intellectual property.

In filing this brief *amicus curiae*, AIPLA takes no position on the merits of Petitioner's claimed rights in the patents in suit. AIPLA's sole interest is in the correct rule of law for obtaining and assigning patent rights, and in the need to ensure that the patent law continues to provide the incentives that serve the Constitutional purpose of promoting the progress of science and the useful arts in accordance with Article I, Section 8.

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[1] In accordance with Supreme Court Rule 37.6, this brief was not authored, in whole or in part, by counsel for a party, and so such counsel or party made any monetary contribution to fund the preparation or submission of this brief.

After reasonable investigation, AIPLA believes that (a) no member of its Board or Amicus Committee who voted to prepare this brief, or any attorney in the law firm or corporation of such a member, represents a party to this litigation in this matter, (b) no representative of any party to this litigation participated in the authorship of this brief, and (c) no one other than AIPLA, or its members who authored this brief and their law firms or employers, made a monetary contribution to the preparation or submission of this brief.

The parties to this litigation have consented to the filing of this brief. Their consent letters have been filed with the court.

SUMMARY OF ARGUMENT

Universities have no "statutory right" under the Bayh-Dole Act, 35 U.S.C. §§ 200-212, to have the title in Federally-funded inventions transferred to them "automatically" or by operation of law. Instead, the Act allocates rights as between the Government and the university as a Federal contractor, and requires proper contractual agreements to be entered into between both the university and Government agency on the one hand, and the university and its inventors on the other. Thus, while the Petitioner frames the question before this Court as whether university inventors can "terminate[] unilaterally" the university's "statutory right" to inventions arising under Federal funding, AIPLA argues that the question is whether title properly vested in Petitioner in the first place. Petitioner argues that the Act supersedes or preempts contractual assignments of inventions, patent applications, and issued patents. However, this position is contrary to the plain language of the statute and its implementing regulations, as well as the historical background, legislative history, and context of the Act within the Federal procurement system. The Act and its implementing regulations preserve and bolster a Federal procurement contracting regime that would be confused and disrupted by Petitioner's interpretation of the Act. In particular,

the "statutory right" is only a default contracting rule that grants title in Federally funded inventions to the university as a Federal contractor. Such title can be contracted around by the Federal agency in any particular situation under four categories of exceptions. Further, in all cases, the title allocation rules are also subject to other provisions of the Act, including those that must be incorporated into funding agreements. Accordingly, the Act primarily establishes a regulated contracting regime, within and consistent with the broader Federal contracting and procurement system, wherein title allocation in any particular instance can be determined only by interpreting the Federal funding agreement and assignment agreements (or lack thereof) from the inventors.

I. The statutory language of the Act and its implementing regulations do not support an interpretation that title is transferred automatically or by operation of law from inventors simply because an invention arose under Federal funding. The Act provides a statutory framework for contractors to *retain* whatever title they have in an invention arising under Federal funding, as determined by the provisions of the relevant funding agreement. It does not directly effectuate an assignment of title from the inventors to either the university contractor or the Federal agency. Further, neither the funding agreements nor the relevant patent clauses promulgated and required for use under the Act's implementing regulations directly effectuate the assignment of invention title from inventors to either the university contractor

or Federal agency. Instead, the foregoing require the university contractor to secure invention title and patent procurement rights from inventors, sufficient to protect the Government's interests in the inventions and any issuing patents under the Act.

II. The historical background, legislative history, and context of the Act within the Federal procurement system all support an interpretation that university contractors must secure invention assignments from inventors.

III. U.S. patent law has always mandated that inventorship and initial title to patentable inventions lies with the true and original natural person inventors. There has never been a provision within U.S. patent law for inventorship and initial title to vest with a non-natural legal person such as a corporation. Accordingly, title must in all cases be transferred by a proper assignment from the natural person inventors for a purported transfer of ownership to other natural or legal persons. Nothing in the Act supersedes this bedrock principle of U.S. patent law.

IV. Assignments of inventions, issued patents, and patent applications are generally governed by a combination of Federal and state common law. Except for cases involving the "hired to invent" doctrine and possibly some narrow Federal statutes allocating title for inventions within a specific field of technology of high importance for national security purposes, all assignments of invention, patent, and patent application title must be in writing to be effective

and enforceable. The Act neither supersedes nor preempts this common law with regard to such assignments. At the same time, inventors affiliated with a university are rarely, if ever, "hired to invent" within the meaning of that common law rule. Thus, in nearly all cases universities will need a written assignment agreement from inventors to secure title, which may then be "retained" as against Government claims under funding agreements.

V. Interpreting the Act to transfer title from inventors by operation of law would amount to a massive and broad-based taking of effectively indeterminate bounds.

VI. Universities are well able to secure the necessary rights under assignment agreements with inventors, and indeed must do so to protect their own and other funders' interests in research results at the university, whether produced under Federal funding or otherwise. It is argued that universities could not secure title to inventions arising from university research *without* a supervening intervention of Federal law assigning title by operation of law. However, that argument effectively means that universities cannot secure title by their own devices for *any* research, whether done under Federal funding or otherwise. If this is true, then it has profound implications for funders and licensees of inventions arising from university research and means that there can be no certainty of title *unless* there is some act of Federal statutory law that supersedes or preempts all other relationships. Thus, even if this Court adopts Petitioner's interpretation of the Act, Petitioner has

now committed itself to the position that title to all non-Federally funded inventions is hopelessly uncertain, which would come as a distressing surprise to university funders and licensees. Therefore, this Court should not feel pressured to address the chain of title responsibilities of universities—or other Federal contractors— in the limited field of Federally-funded inventions. Lawful and adequate contractual and record-keeping measures on chain of title are available to universities.

ARGUMENT

I. THE STATUTORY LANGUAGE OF THE ACT DOES NOT SUPPORT AN INTERPRETATION THAT TITLE IS TRANSFERRED AUTOMATICALLY OR BY OPERATION OF LAW FROM INVENTORS SIMPLY BECAUSE AN INVENTION AROSE UNDER FEDERAL FUNDING.

The Act provides a statutory framework for contractors to *retain* whatever title they have in an invention arising under Federal funding, as determined by the provisions of the relevant funding agreement. "Each nonprofit organization or small business firm may, within a reasonable time after disclosure . . . elect to *retain* title to any subject invention." 35 U.S.C. § 202(a) (2006) (emphasis added). There is nothing in the Act that states that it is transferring title from inventors (who are legally distinct persons from the nonprofit organization or small business firm that might employ or contract with them) to either the

university contractor or the Federal agency. The statute does not say, for example, that the nonprofit organization or small business firm may elect to *take* title from the inventors.

Further, neither the funding agreements nor the relevant patent clauses promulgated by the Department of Commerce and required for use under the Bayh-Dole implementing regulations, 37 C.F.R. § 401.14 ("Standard Patents Rights Clauses"), directly effectuate the assignment of invention title from inventors to either the university contractor or Federal agency. To the contrary, the Standard Patents Rights Clauses require the contractor (the nonprofit organization or small business firm that has entered into a Federal funding agreement incorporating the Clauses) to enter into written agreements to secure the Government's rights under the Act. "The *contractor* agrees to require, by written agreement, its employees, other than clerical and nontechnical employees, . . . to execute all papers necessary to file patent applications on subject inventions *and* to establish the government's rights in the subject inventions." 37 C.F.R. § 401.14(a), *Patent Rights (Small Business Firms and Nonprofit Organizations)*, §(f)(2) (first emphasis in original, second emphasis added). Both prongs of this contractual requirement would be unnecessary if the Act automatically vested title to the invention in the contractor by operation of law. The contractor would not even have to obtain the assent or participation of the inventor, as it could file the patent application under the "hostile inventor"

provision of 35 U.S.C. § 118.[2] Even if the first prong were read simply as a means to smooth the path for perfecting and/or recording title assignment with the U.S. Patent and Trademark Office ("USPTO"), this would not explain the presence of the second prong. Written agreements with employee-inventors to protect the Government's rights in such inventions would be entirely superfluous if the Act vested title in the contractor by operation of law. It should be noted that the Act's implementing regulations are entitled to *Chevron* deference and were originally charged to the Office of Federal Procurement Policy, further reinforcing that the title allocation system envisioned by Congress was that of the general Federal procurement system, *i.e.*, a regulated contractual regime. *See Chevron U.S.A., Inc. v Natural Resource Defense Council, Inc.*, 467 U.S. 837 (1984).

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[2] "Whenever an inventor refuses to execute an application for patent, or cannot be found or reached after diligent effort, a person to whom the inventor has assigned or agreed in writing to assign the invention or who otherwise shows sufficient proprietary interest in the matter justifying such action, may make application for patent on behalf of and as agent for the inventor on proof of the pertinent facts and a showing that such action is necessary to preserve the rights of the parties or to prevent irreparable damage . . . ." 35 U.S.C. § 118 (2006).

II. THE HISTORICAL BACKGROUND, LEGISLATIVE HISTORY, AND CONTEXT OF THE ACT WITHIN THE FEDERAL PROCUREMENT SYSTEM SUPPORT AN INTERPRETATION THAT UNIVERSITY CONTRACTORS MUST SECURE INVENTION ASSIGNMENTS FROM INVENTORS.

Beyond the clear indications of the Act and its implementing regulations that contractors must secure contractual invention assignments from inventors, the history and context of the Act within the broader Federal procurement system also supports an interpretation that the Act does not transfer title by operation of law. While the Act is sometimes portrayed as an *ex nihilo* event that established university technology transfer when there was none, or at the very least created an entirely new regulatory framework for it, the Act in fact is largely built upon unified existing policies and regulation dating back to the early 1960s. Sean O'Connor *et* al., *Legal Context of University Intellectual Property and Technology Transfer* 7-23 (report prepared for The National Academies, Sep. 20, 2010, http://sites.nationalacademies.org/PGA/step/PGA_058712) [hereinafter "O'Connor"]. These policies themselves were built upon the influential report and recommendations issued by then Attorney General Francis Biddle in 1947. Francis Biddle, Attorney General, Investigation of Gov't Patent Practices and Policies: Report and Recommendations of the Attorney General to the President (1947) [hereinafter "AG Report"]; O'Connor at 7-15.

The AG Report summarized patent law with regard to inventorship and initial ownership as it existed at that time (and which remains the same today) and made clear that Government contractors must have invention title assigned to them:

> Under our law, a patentable invention can be made only by an individual or by several individuals working jointly. Since the Government contractor is usually a corporation or an institution, the latter's agreement to make some or all of the patent rights available to the Government requires a corresponding obligation on the part of the contractors' employees who engage in performing the research contract. Such an obligation is as a general rule imposed expressly by the employment contract.

1947 AG Report, vol. 1 at 78. The AG Report then referenced extensive research done on the actual practices of both private industry and nonprofit research organizations and universities, and concluded that:

> . . . the scientific and technical employees of almost all industrial organizations are under contract to assign their patent rights to the employer, and most academic and other noncommercial institutions likewise require assignment of patent rights by members of their staff who have been detailed to perform research contracts with third parties. Hence the disposition of rights to inventions made under a Government-financed research contract involves the allocation between

> Government and contractor of the power to exclude others from using the invention, or to permit such use upon payment of a royalty or compliance with some other legal condition.

1947 AG Report, vol. 1 at 88. This reliance on contractors' existing practice to secure invention assignments from inventors, and the corollary that Federal policy need only then concern itself with the allocation of title as between Federal agencies and the contractor entity, became a fundamental assumption of Government contracting and procurement policy that continues to this day.

This assumption is also consistent with the past and current practice of organization-to-organization contracting in the private sector. Corporations and other non-natural legal persons usually draft their contracts with each other as the sole parties, i.e., without adding each other's employees as parties to the agreement unless there is some supervening reason to do so. At most, the contracts may impose on each party the obligation to enter into appropriate arrangements with employees to protect the other party's rights under the contract.[3] This tracking of private sector contracting principles for Government policy and contracting purposes paralleled the established law of title

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[3] For example, when confidentiality is a term of the contract, the party owing the duty of confidentiality may be explicitly required to secure an adequate level of confidentiality from the relevant employees. Likewise, where the allocation of intellectual property rights is a term of the contract, the relevant parties may be explicitly required to secure the necessary assignments or licenses from employees.

allocation for inventions by employed inventors. 1947 AG Report, vol. 1 at 78.

The Kennedy Administration was the first to act on the AG Report with regard to extramural research and development ("R&D"). Memorandum for the Heads of Executive Departments and Agencies, 28 Fed. Reg. 10,943 (Oct. 12, 1963), 3 C.F.R. § 861 (1959-1963) [hereinafter "Kennedy Memo"]; O'Connor at 9-10. Its primary purpose was to establish a uniform Government patent title allocation policy for such R&D contracts based upon the recommendations of the AG Report. The Kennedy Memo addressed *only* the allocation as between the Government and contractors. Thus, it clearly appeared to rely on the AG Report's assumption that contractors would secure necessary assignments from employees, and therefore policy need only be made for allocation as between the Government and its contractors. At the same time, the Kennedy Memo expanded the opportunities for contractors to retain title beyond the recommendations of the AG Report and existing practices of a number of Federal agencies. However, it was never implemented in Government-wide regulations, in large part because a number of agency and technology specific patent title allocation statutes had been passed by Congress in the first half of the Twentieth Century. O'Connor at 10-13.

The Nixon Administration essentially reissued the Kennedy Memo, with minor modifications primarily intended to increase further the opportunities for contractor retention of title. Memorandum for Heads of Executive Departments and Agencies on Government Patent Policy, 36 Fed.

Reg. 16,887 (Aug. 31, 1971) [hereinafter "Nixon Memo"]; O'Connor at 13. The Nixon Memo thus also addressed only allocation of title as between the Government and contractors, continuing the assumption of, and reliance on, contractors securing appropriate title rights from employee-inventors. Despite the continued existence of the *ad hoc* invention title allocation statutes, the Nixon Administration directed the General Services Administration ("GSA") to promulgate Government-wide patent title allocation regulations to implement the Nixon Memo. GSA issued an interim version of the regulations in 1973 and a final version in 1975. O'Connor at 13-14. These regulations were also then built upon the premise of contractor responsibility for securing title rights from employees, and now explicitly require contractors to secure the rights by mandating the inclusion of different versions of a Patent Rights Clause, depending on the exact funding circumstances, in all Federal extramural R&D contracts. Federal Procurement Regulations §§ 1-9.107, 1-9.107-5(a)-(c) (Patent Rights-Acquisition by the Government, Subsection (e)(3)),1-9.107-6(a)-(b) (Patent Rights—Acquisition by the Government (Short Form), Subsection (e)(1)) ("The Contractor shall obtain patent agreements to effectuate the provisions of this clause from all persons in his employ who perform any part of the work under this contract except nontechnical personnel, such as clerical employees and manual laborers."); GSA, Federal Procurement Regulations, Part 1-9, Patents, Data and Copyrights: Allocation of Rights in Inventions, 40 Fed. Reg. 19,814 (May 7, 1975).

Developing alongside these formal policies and regulations was the Institutional Patent Agreement ("IPA") system used by agencies and departments, including the National Institutes of Health, the then Department of Health, Education, and Welfare, and the National Science Foundation. O'Connor at 11-16; John H. Raubitschek and Norman J. Latker, *Reasonable Pricing—A New Twist for March-In Rights Under the Bayh-Dole Act*, 22 Santa Clara Comp. & High Tech. L.J. 149, 153 (2005); Gov't Patent Policies: Institutional Patent Agreements, Hearings before the Senate Subcomm. on Monopoly and Anticompetitive Activities of the Select Comm. on Small Bus. (95th Cong., 2d Sess., May 22, 1978). The IPAs were master agreements between research or higher education institutions and Federal agencies that set forth the patent allocation terms for all research funded at the institution by the agency. Similar to the GSA regulations and governed by them after they were promulgated,, the IPAs expressly placed the burden of securing patent rights from inventors on the contractor. The IPA concept originated in the 1950s, predating both the Kennedy Memo and the GSA regulations. A publicly available version of a standard form of IPA from 1978 includes a good example of the explicit clause requiring the contractor to secure rights from inventors in conformance with the then governing GSA regulations.[4]

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[4] "The Institution shall obtain patent agreements to effectuate the provisions of this Agreement from all persons in its employ who perform any part of the work under any contract except nontechnical personnel, such as clerical and manual laborers." Institutional Patent Agreement, § V(b), U.S. Senate, Hearings

By the time the Bayh-Dole Act was passed in 1980, the Federal Procurement Regulations system was well established, and the requirements for Federal extramural R&D contracts were embedded within and governed by it. However, despite efforts to create uniform Government-wide patent policies, there remained *ad hoc* patent allocation statutes across the U.S. Code. The variability that they enabled or mandated for different Federal department and agency extramural research policies resulted in a patchwork of different bureaucratic systems and rules for funding agreements. Overall, the tendency was still to require contractors to assign title to the Federal funding agency, although this was by no means universal. The Act then was intended to establish a truly uniform Government-wide statutory default rule of contractor retention of title, limited to nonprofit organization and small business contractors. Crucially, it facilitated this by explicitly superseding the *ad hoc* title allocation statutes. 35 U.S.C. § 210 (2006). There is no evidence that this section was intended to change any other legal relationships or the initial vesting of title in natural person inventors. Changing the latter would have entailed a profound revision of established practice and Federal and state law, warranting at least some discussion in the legislative history, of which there is none. Instead, § 210 was necessary simply to supersede the existing *ad hoc* statutes only

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Before the Subcomm. on Monopoly and Anticompetitive Activities of the Select Comm. on Small Business, 95th Cong. (May 22, 23, June 20, 21, and 26, 1978) (Part 2: Appendix: GSA submission for the record: Minutes of meetings of interagency committees on revision of the draft of the Government-wide IPA (notes omitted), pp. 1831-43).

to the extent that they would require "a disposition of rights in subject inventions *of small business firms or nonprofit organizations contractors* in a manner that is inconsistent with this chapter . . . ." 35 U.S.C. § 210 (2006) (emphasis added). The intent was still to allocate title rights only as between the Federal agencies and their nonprofit and small business contractors. Accordingly, the quoted language limits itself to inventions *of* the contractors, *i.e.*, those to which they hold good title.

Thus, the first step in analyzing the effect of § 210 on any particular situation is to determine whether the small business firm or nonprofit organization contractor holds title to the invention. This, in turn, relies on determining whether the contractor has secured assignment of the invention from the inventors. If it has, then the allocation of title is, according to the Act's rules, as specified in the funding agreement. If the contractor does not hold title to the invention, then the title allocation will be determined according to the underlying statute, to the extent it is still in effect and applicable. Section 210 is open-ended with regard to which other statutes it supersedes ("including but not necessarily limited to") only because it anticipated that other statutes might be identified later, and future statutes might be passed, which affect title allocation as between small business firms and/or nonprofit organization contractors. 35 U.S.C. § 210 (2006) ("The Act creating this chapter shall be construed to take precedence over any future Act unless that Act specifically cites this Act and provides that it shall take precedence over this Act").

Nothing in the legislative history of the Act indicates that it was intended to change the standard Federal Procurement Regulations rules *other than* to institute a default rule of contractor title for small business and nonprofit contractors (as between the contractor and Federal funding agency). Similar to the Kennedy Memo and Nixon Memo, the Act and its legislative history focus only on the allocation of title as between the contractor and the Federal funding agency.[5] This is again because both the standard practice of securing assignments from employee-inventors was asserted to be settled and the GSA regulations had established an explicit requirement for such assignments in the patent rights clauses mandated for use in *all* extramural R&D contracts. Thus, for example, even where there is a reference to the Act "automatically" granting title to small businesses and nonprofits (subject to agency invocation of the exceptions to the default rule) in the Senate Report that serves as the primary legislative history for the Act, S. Rep. 96-480 at 36, this comment is directed to the fact that the Act was intended to change the existing *ex post* determination of title allocation as between contractor and Federal agency into an *ex ante* system in which the allocation was predetermined under the funding agreement (and hence was "automatic").

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[5] With the exception of the mandatory sharing of royalties with inventors in the case of nonprofit contractors, 35 U.S.C. § 202(c)(7)(B) (2006), discussed in Part V *infra*, and the process for granting title back to inventors where contractors had originally secured title rights from the inventor, but then chose not to elect rights as against the federal funding agency under the Act, 35 U.S.C. § 202(d) (2006).

As discussed above in Part I, the Act's implementing regulations continued the GSA regulations' explicit requirement for contractors to secure patent rights from employee-inventors. Further, the Act's implementing regulations broadly tracked the earlier GSA regulations, creating a chain of continuity in the basic administration and content of the R&D procurement system, even for provisions not expressly required by the Act, and including the continuation of mandatory standard patent rights clauses. O'Connor at 15-23.

III. U.S. PATENT LAW HAS ALWAYS MANDATED THAT INVENTORSHIP AND INITIAL TITLE TO PATENTABLE INVENTIONS LIES WITH THE TRUE AND ORIGINAL NATURAL PERSON INVENTORS.

Under the U.S. Constitution, Art. 1, § 8, cl. 8, and § 101 of the Patent Act, 35 U.S.C. § 101, both inventorship and initial ownership of patents vest only in natural person inventors who actually invent the subject matter: "*Whoever invents or discovers* any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101 (2006) (emphasis added). Further, under § 102:

> A *person* shall be entitled to a patent unless . . .
>
> (c) he has abandoned the invention, or

> (f) he did not himself invent the subject matter sought to be patented.

35 U.S.C. § 102 (2006) (emphasis supplied).

These provisions, taken together and with various other provisions, have consistently led leading commentators to conclude that both inventorship initial ownership vest *only* in natural person inventors, and not in non-natural legal persons, such as corporations:

> At the heart of any ownership analysis lies the question of who first invented the subject matter at issue, because the patent right initially vests in the inventor who may then, barring any restrictions to the contrary, transfer that right to another, and so forth.

Beech Aircraft Corp. v. EDO Corp., 990 F.2d 1237, 1248 (Fed. Cir. 1993); *see also* Donald S. Chisum *et al.*, Principles of Patent Law: Cases and Materials 1235 (3d ed., Foundation Press, 2004).

By contrast, U.S. copyright law expressly allows for non-natural legal persons, such as corporations, to be "authors" in the context of works-made-for-hire. 17 U.S.C. §§ 101, 201(b) (2006). Thus both authorship and initial ownership of works-made-for-hire vest in the employer or commissioning agent, even if that is a non-natural legal person such as a corporation. In other words, authorship and ownership need never "pass through" a natural person who actually creates the work-made-for-hire. U.S. patent law does not now, and never has had, a similar doctrine. Rather, inventorship and ownership must always "pass

through" the natural person inventors who actually invent the subject matter.

However, patents and patent applications are given the attributes of personal property under the Patent Act, 35 U.S.C. § 261 (2006), and thus can be assigned or transferred just like any other property (subject to some limitations in the Patent Act). Such assignments can even be "prospective" in that they can convey title to patents yet to be issued, or applications yet to be filed, on inventions yet to be created. In fact, so long as a proper assignment has occurred, assignees can file applications on the inventor(s)' behalf, with or without the inventor(s)' direct involvement. 35 U.S.C. § 118 (2006). Such assignment may take the form of a written agreement between the parties, a specific statutory obligation to assign (as discussed *infra* in Part IV), or an equitable obligation to assign under the "hired to invent" doctrine (also discussed *infra* in Part IV). Under any of these mechanisms, the patent may be issued directly to the assignee. 35 U.S.C. § 152 (2006). Yet, none of the foregoing change the requirement that inventorship and ownership must still "pass through" the natural person inventors first. In fact, inventorship must always remain with the natural person inventors—in that they must all and only always remain listed on the issued patent—on pain of invalidation of the patent. 35 U.S.C. § 116 (2006).[6] In sum, the foregoing underscore that

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[6] Errors of misjoinder (individuals listed as inventors who in fact did not make a substantial contribution to the invention) and nonjoinder (failure to list an individual who did make a substantial contribution to the invention) can, and must, be

inventorship and ownership must always start with the natural person inventors, in clear contrast to the work-made-for-hire doctrine in U.S. copyright law.

IV. ASSIGNMENTS OF INVENTIONS, ISSUED PATENTS, AND PATENT APPLICATIONS ARE GENERALLY GOVERNED BY A COMBINATION OF FEDERAL AND STATE COMMON LAW.

Because inventions, patent applications, and issued patents are treated as personal property under 35 U.S.C. § 261, title to such property can be freely transferred like other personal property. *See id.* In most cases, this transfer of title will take the form of a written assignment agreement. As a contract, this agreement will in large part be governed and interpreted by state contract law. However, because such assignments also bear directly on questions of standing to sue on the patent, the U.S. Court of Appeals for the Federal Circuit ("Federal Circuit") has held that it can develop Federal case law on the matter. *DDB Techs., L.L.C. v. MLB Advanced Media, L.P.*, 517 F.3d 1284, 1290 (Fed. Cir. 2008). Nonetheless, this developing case law of the Federal Circuit appears to rely on standard principles of common law contract and property. It fills in interstitial gaps important and specific to patent assignment and licensing contracts rather than supplanting

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remedied under special provisions in the Patent Act for this purpose. 35 U.S.C. § 256 (2006).

common law principles with inconsistent or contrary rules or principles.

Similarly, this Court has established case law on the allocation of invention title between employers and employees in the absence of a written agreement that is largely consistent with the existing common law rules. *U.S. v. Dubilier Condenser Corp.*, 289 U.S. 178 (1933). This tripartite invention allocation framework is often, and somewhat misleadingly, referred to collectively as "shop rights" and was developed from Nineteenth Century case law. The first part is the true shop right: where an employee uses his employer's resources or time to invent, the employee may retain title, but must grant a perpetual, non-exclusive license to the employer. This license is not transferable and questions have arisen as to whether it can even survive any change of control of the firm. The second part is the "hired to invent" doctrine. Where the employee was specifically hired to invent the sort of thing ultimately invented, this doctrine equitably vests title to the invention in the employer. The challenge with this rule is the evidentiary support required of employers to show that an employee was specifically hired to invent the kind of thing invented and on which the employer is now making an equitable claim to title. The third part has no specific name, but is where the employee invents on his own time and with his own resources, and was not hired to invent that kind of thing. In this case, the employee retains the title free and clear, with no license necessarily granted to the employer (unless the employee decides to grant one).

The only other binding law on the assignment of title to inventions, patent applications, and issued patents is the collection of *ad hoc* title allocation statutes, superseded by the Act as discussed in Part II above. An analysis of the background, implementation, and interpretation of these statutes is well beyond the scope of this brief. Thus, AIPLA does not attempt to answer whether these statutes divested third party inventors (*i.e.*, those not in privity with the Government) of title to their inventions without regard to whether assignment agreements were in place or the inventors were "hired to invent," or whether they operated similarly to the broader category of Federal R&D contracts that relied on contractors to secure title rights from employee-inventors. Even if these statutes are properly construed to have divested title from inventors by operation of law—*i.e.* without an assignment agreement or "hired to invent" relationship—they are limited to narrow areas of exceptional national interests such as national security, atomic energy, and space exploration.[7] These statutes included unambiguous language stating that the invention would be transferred from the *inventor* and giving special provisions for how the USPTO should process any application claiming an invention in the field of technology. Bayh-Dole contains no such language and therefore title must be transferred from the inventors for inventions arising under Federal funding by a proper assignment agreement.

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[7] See, for example, rights of the Atomic Energy Commission at 42 U.S.C. § 2182 and rights of the National Aeronautical and Space Administration at 42 U.S.C § 2457(a)(2).

V. INTERPRETING THE ACT TO TRANSFER TITLE FROM INVENTORS BY OPERATION OF LAW WOULD AMOUNT TO AN UNCONSTITUTIONAL, PERPETUAL, AND EFFECTIVELY INDETERMINATE STREAM OF TAKINGS FROM UNIVERSITY INVENTORS

Federal funding is involved in an enormous amount of university research. Such research is not limited to any particular fields of science, technology, or arts. Further, the range of faculty, staff, students, and non-employee individuals involved in such research may be as broad as the range of such personnel involved in the university enterprise generally. Petitioner's interpretation of the Act presumes that Congress authorized the Government to engage in an effectively indeterminate stream of takings of private property—the initial title of inventors to their inventions, patent applications, and issued patents—with no explicit provision for due process or fair compensation, rendering it unconstitutional. The scope of such takings would be determined only by the question of whether Federal funding was used, even if only in small part, for the research that led to the invention.

Such a massive and broad-based system of takings was not part of the pre-Bayh-Dole Federal R&D procurement system. While there were intense debates over the merits of the "title" vs. "license" positions, the Government's rights to either were established by *contract* not by statute. The AG Report recommended a title policy for all but

exceptional cases; it argued this based on the Government's "equity" in inventions to which it had contributed funding. But nothing in the Report argued that the Government had a *legal* right to this "equity" other than whatever contractual rights (and implied contract rights) specific Federal funding agencies had negotiated with the contractors with which they were directly in privity. The issue instead was what patent title policy the various Federal agencies should adopt in negotiating funding agreements with contractors. This is little different from the decision any private party must make when funding or investing in research that might lead to patentable inventions.

Further, the AG Report expressly considered whether contractors would be able to deliver title from their employee inventors and concluded that most contractors in fact already had patent assignment agreements in place with relevant employees. Accordingly, the AG Report relied on such contractor employee assignment agreements in restricting its focus to the merits of title vs. license policies *only* with regard to the Government and contractor. As discussed in Part II above, the subsequent extramural R&D patent policies of the Kennedy and Nixon Administrations explicitly required that contractors secure agreements from their inventive employees in order to protect the Government's rights. This system was incorporated directly into the Act and its implementing regulations, which remain in effect to this day.

Petitioner's position is undermined by the Government's right to practice privately held patents without authorization under 28 U.S.C. § 1498. First,

the Government is not authorized to take *title* to the patents, but only to *practice* the patented invention. Second, the statute expressly provides that patent owners whose exclusive rights are infringed by such actions may seek fair compensation for such use in the Court of Federal Claims. There is no such provision in the Bayh-Dole Act to compensate for the even greater encroachment that results from Petitioner's position that the Act "automatically" transfers title from the inventors to the contractor by operation of law. The inventor's "right" to share in the royalties arising from her invention under § 202(c)(7)(B) cannot serve this function for two reasons. First, this subsection applies *only* to nonprofit contractors, which would mean that a completely *uncompensated* taking would be authorized with regard to employee inventors of small business contractors. Second, the nonprofit/university inventor's right to share in the royalties has been held to not require any fixed ratio or even minimum rate or amount.[8] *Platzer v. Sloun-Kettering Institute*, 787 F. Supp. 360, 365, 367-368 (S.D.N.Y. 1992). Accordingly, this can hardly be said to satisfy the constitutional requirements of due process and *fair* compensation for Federal takings.

Such minimal or nonexistent compensation might be justified by the fact that the Government is providing funding for the research leading to the invention, except that the Government is not paying the inventor directly. Rather it is funding the contractor, which may or may not in turn be

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[8] Indeed, the Department of Commerce declined to specify any rates, ratios, or minimums for this revenue sharing in the Act's implementing regulations. O'Connor at 35.

transferring any part of the research funding to the inventor (other than to support the research). Contrast this with the normal intellectual property rights assignment or "hired to invent" employment scenarios. These give rise to invention assignments in which inventors are being compensated for their assignments in part of the regular employment compensation.[9] But few faculty are "hired to invent" within the meaning of that doctrine, in that they are hired to research and teach generally, but are not directed to solve specific problems. Their inventions are generally incidental to their faculty obligations of teaching, research, and service. Finally, a number of universities do not have general obligations or expectations for all faculty to assign all inventions that might arise during the term of employment. In these cases, faculty members would receive no compensation or consideration for assigning their inventions other than the potential for some statutorily undefined share of royalties. This would seem to be an unconstitutional taking with neither due process nor fair compensation.

An interpretation of the Act as a contracting regime, as argued by AIPLA, avoids these thorny constitutional issues. Under the contract approach, the Federal agency negotiates and executes a funding agreement with a university contractor, within the statutorily defined parameters, which in turn requires the contractor to enter into (or have in place already) appropriate contracts with its various

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[9] One may argue whether such compensation is fair to the employee for her invention. But that is a matter of labor markets and employment negotiations, not a statutory directive.

faculty, staff, students, and affiliated inventors to secure the Government's rights. This is in the contractor's interest anyway, as it should be protecting its own rights by contract with inventors, as discussed further in Part VI below. It would be foolhardy for the university to instead rely on the hired to invent doctrine to secure its own interests especially with regard to the majority of faculty and students who have not been hired to invent within the meaning of that doctrine. This approach is also far more consistent with the general Federal procurement system than Petitioner's position premised on an effectively indeterminate massive stream of unconstitutional takings.

VI. UNIVERSITIES ARE WELL ABLE TO SECURE THE NECESSARY RIGHTS UNDER ASSIGNMENT AGREEMENTS WITH INVENTORS, AS THEY ALREADY MUST PROTECT THEIR INTERESTS IN INVENTIONS ARISING FROM UNIVERSITY RESEARCH.

Petitioner argues that this Court must adopt their interpretation of the Act or else they would not be able to secure the Government's rights in Federally-funded inventions nor be able to assure prospective licensees of clear chain of title in such inventions. Admittedly, tracking the contributions of a number of different researchers over time, as well as monitoring those researchers' consulting and other external activities is challenging. But this is equally true for non-Federally funded research as it is for Federally funded research.

Petitioner therefore commits itself to a proposition sure to distress its licensees and other funders: it cannot ensure clear chain of title to the inventions it purports to own *without* the supervening intervention of a Federal law assigning title from inventors by operation of law. Because many university inventions arise outside of Federal funding, then such a supervening statute is not even arguably available for those inventions.

Reports of "backdoor" inventions that wind up being patented outside of the university because university personnel simply fail to disclose them to the university are not unique to universities. Nonprofit research institutions, private firms, and even the Government all face similar problems. What may differ are: the culture of employment agreements; the possibility of invoking "hired to invent" equitable claims; and the willingness and ability of the organization to enforce its assignment rights. But the contractual rules for establishing ownership and control of inventions are applicable to all organizations. Thus, universities are no less able to secure the necessary assignments from inventors than are private firms, other nonprofit research institutions, and the Government. Indeed, they must already do so to protect their own interests in patentable research results, whether produced under Federal funding or not. Accordingly, this Court should not feel pressured to address the chain of title responsibilities of universities—or other Federal contractors— in the limited field of Federally-funded inventions. The same contractual mechanisms which universities must use to protect their own interests can and

must—under a proper interpretation of the Act and its implementing regulation—be used to protect the Government's interests as well.

Specifically, universities should use contractual assignment provisions for present assignments of a defined class of future inventions, or should use conditional agreements to assign where the university requires the inventor to add clauses to all third party agreements that establish the university's senior claims to a defined class of inventions. Present assignments, sometimes called "prospective" assignments, effectuate an immediate transfer of ownership rights to future inventions. These can be limited to defined classes of inventions, *e.g.*, "inventions arising from Federally funded research." Such an approach can preserve the flexibility desired by some universities to avoid appropriating all faculty inventions in favor of only receiving title to certain kinds of inventions. If the university still wants to use a conditional assignment agreement, *i.e.*, one that only effectuates an obligation to assign inventions in the future, it can do so as long as it requires researchers to include "supremacy" intellectual property clauses in agreements for any outside consulting or other activities that might give rise to patentable inventions. Such an approach was recently upheld in *Cephalon, Inc. v. Johns Hopkins University*, 2009 WL 4896227 (Del. Ch. 2009). Accordingly, universities are well able to secure the necessary rights to protect their own and the Government's interests and rights.

Admittedly, some inventions will slip through even with the best arrangements in place.

This is regrettable, but it is not the end of the world. Many, if not most, inventions arising in university research will prove not to be valuable to anyone, and may never be commercialized simply for business reasons. The specter raised by the Petitioner and others is that a steady stream of valuable and/or socially critical inventions arising under Federal funding will improperly flow out to private ownership without passing through the proper Bayh-Dole allocation system. Under the Federal Circuit's ruling below, title to such an invention may be irretrievably lost if a superior assignment claim is made by an outside individual or entity over the university's assignment claim. As pointed out by the Federal Circuit, however, the university will still have breach of contract claims against the researcher who appears to have improperly assigned the invention. It is true that a suit based on these claims may be impractical as a way to recover any substantial damages or because of the effects such a suit could have on university employee morale and public relations. But those considerations do not moot the claims and universities may find such suits more practical in some cases that others.

In sum, while it does seem odd that an inventor can intentionally or inadvertently subvert the intended title allocation system of the Act, this risk must be balanced against the risks of alternative title allocation systems that Congress might have enacted, particularly that advocated by the Petitioner. Congress appears to have chosen a flexible contract-based system in line with the GSA regulations and IPAs and in conformance with the

general Federal procurement system. This system also respects the bedrock principle of U.S. patent law that inventorship and ownership in all cases start with the natural person inventors and respects the free market, contract-based assignment system for inventions.

The risk of failed contractual performance and occasional lost title is arguably mitigated both by the longstanding reliance on the contractor practice of securing proper title agreements (as first established in the AG Report) and by the benefits of a flexible contract-based system. This contrasts with the rigidity of an automatic title allocation system that transfers title by operation of law, which invites constitutional challenges based on Government takings from an undefined class of inventors across an effectively indeterminate range of inventions.

Regardless of whether one ultimately agrees with the policy, it is clear that the decision by Congress was a reasonable one, firmly rooted in existing practice and the Federal procurement system, yet with a different contractual default rule. Overall, the system seems to have achieved its goals admirably. It should not now be disrupted by revisionist history of the Act and an unusual fact pattern.

CONCLUSION

For all these reasons, AIPLA respectfully requests that the Court clarify the decision of the Federal Circuit.

Respectfully submitted,

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AMICUS CURIAE BRIEF

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In the Supreme Court of the United States

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, PETITIONER

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF AMICI CURIAE ASSOCIATION OF AMERICAN UNIVERSITIES, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, AMERICAN COUNCIL ON EDUCATION, ASSOCIATION OF AMERICAN MEDICAL COLLEGES, ASSOCIATION OF INDEPENDENT RESEARCH INSTITUTES, ASSOCIATION OF PUBLIC AND LAND-GRANT UNIVERSITIES, THE ASSOCIATION OF UNIVERSITY TECHNOLOGY MANAGERS, COUNCIL ON GOVERNMENTAL RELATIONS, IN SUPPORT OF PETITIONER

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UNIVERSITY OF NEBRASKA-LINCOLN, UNIVERSITY OF NEW HAMPSHIRE, THE BOARD OF REGENTS OF THE NEVADA SYSTEM OF HIGHER EDUCATION, ON BEHALF OF THE UNIVERSITY OF NEVADA, LAS VEGAS, THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL, UNIVERSITY OF NOTRE DAME, THE UNIVERSITY OF OKLAHOMA, UNIVERSITY OF PENNSYLVANIA, UNIVERSITY OF PITTSBURGH, UNIVERSITY OF ROCHESTER, UNIVERSITY OF RHODE ISLAND, UNIVERSITY OF SOUTHERN CALIFORNIA, UNIVERSITY OF TENNESSEE, KNOXVILLE, THE UNIVERSITY OF TEXAS AT AUSTIN, UNIVERSITY OF VIRGINIA, UNIVERSITY OF WASHINGTON, BOARD OF REGENTS OF THE UNIVERSITY OF WISCONSIN SYSTEM, WASHINGTON STATE UNIVERSITY, WAYNE STATE UNIVERSITY, WASHINGTON UNIVERSITY IN ST. LOUIS, WISCONSIN ALUMNI RESEARCH FOUNDATION, AND YALE UNIVERSITY

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INTEREST OF AMICI CURIAE

Amici are research universities, independent research institutes, and associations of researchers and research institutions that collectively account for the vast majority of federally funded research performed pursuant to the Bayh-Dole Act, 35 U.S.C. 200 *et seq.* Amici are keenly aware of the threat the court of appeals' decision poses to Bayh-Dole's success.[1]

SUMMARY OF ARGUMENT

The Bayh-Dole Act, adopted in 1980, has for thirty years provided the basis for an immensely successful collaboration between the federal government, universities, and private industry whereby federally funded inventions are transformed into jobs and products that improve the lives of all Americans. The cornerstone of Bayh-Dole is the statutory policy granting universities the right to retain title to inventions conceived in the course of federally funded research programs.

Stanford, exercising its rights under Bayh-Dole, elected to retain ownership of an invention made by several Stanford researchers pursuant to research funding from the National Institutes of Health (NIH) for testing the effectiveness of anti-HIV therapies. The Federal Circuit held Stanford's exercise of its Bayh-Dole rights was ineffective to give it ownership of the

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[1] Pursuant to this Court's Rule 37.6, amici state that no counsel for any party authored this brief in whole or in part, and that no person or entity other than amici or their counsel made a monetary contribution to the preparation or submission of this brief. The parties have consented to the filing of this brief, and letters evidencing such consent have been filed with the Clerk of this Court, pursuant to this Court's Rule 37.3.

interests of one of the Stanford co-inventors, Mark Holodniy, because Holodniy had previously assigned his future inventions to a private firm, Cetus.

A. Roche defends the court of appeals' decision by asserting that there is a background presumption that researchers who make inventions with federal funding have a "basic freedom to assign" those inventions to third parties and that Bayh-Dole does not clearly displace that background norm. Br. in Opp. 2, 18. But the historical record is to the contrary. For at least 60 years, title to federally funded inventions has been disposed of by operation of law. Under an Executive Order, the inventions of federal employees are assigned by operation of law to the employing agency. Numerous statutes and regulatory frameworks, including several statutes specifically referenced in Bayh-Dole, also provide for disposition of rights in federally funded inventions by operation of law. Thus, when Congress adopted Bayh-Dole, it did so against a clear historical backdrop that rights in federally funded inventions could not be freely assigned by inventors, but were instead to be disposed of by operation of law.

B. Roche contends that a ruling in Stanford's favor would "confiscate [Cetus's] intellectual property" because the inventions were "conceived before Holodniy left Cetus." Roche Supp. Pet. Br. 2. Roche's assertion mischaracterizes the premise of the Federal Circuit's decision. The Federal Circuit made clear that its ruling applies *even if* Stanford's inventions were "conceived and reduced to practice" by Stanford inventors with federal funding *after* Holodniy left Cetus. Pet. App. 15a, 18a-21a. In other words, the Federal Circuit did not grant Cetus rights based upon its purported contribution to the invention. Rather, the Federal Circuit

established a categorical rule that would allow university researchers, whether intentionally or by oversight and without the university's awareness, to assign federally funded inventions to any third party, even one with no connection to the invention.

C. The Federal Circuit's decision casts doubt on the rights of universities and the federal government alike to inventions arising from hundreds of billions of dollars in federally funded research. By making ownership of federally funded inventions turn on assignments in undisclosed documents that may have been signed many years before the federally funded research in question, the court of appeals' decision makes it virtually impossible for universities or their prospective industry licensees to be certain that the university actually owns the invention in question. That uncertainty cannot be cured by changing the language of university researcher agreements. Hundreds of billions of research funding dollars have already been invested pursuant to existing contracts. By introducing uncertainty regarding university title, the decision below undermines Bayh-Dole's objective to facilitate the commercialization of federally funded inventions.

ARGUMENT

I. Consistent With Longstanding Precedent, Bayh-Dole Disposes Of Rights In Federally Funded Inventions By Operation Of Law, And Inventors Are Not "Free To Assign" Them To Third Parties

Roche maintains that Bayh-Dole cannot provide the controlling framework for disposing of rights to the patents-in-suit because, in Roche's words, "the Bayh-Dole Act nowhere alters an inventor's basic freedom to assign his own rights in an invention to a third party." Br. in Opp. 2. See Roche Supp. Br. 12 n.6. Roche contends that there is a background presumption that researchers who make inventions with federal funding have a "basic freedom to assign" those inventions and that Bayh-Dole does not clearly displace that background norm. Br. in Opp. 2, 18.

The factual predicate for Roche's contention is mistaken. By statute, Executive Order, and regulation, the federal government has dictated the disposition of rights in federally funded inventions for at least 60 years, and individual inventors are not free to assign those inventions to third parties.

Like its predecessors, Bayh-Dole provides for the "[d]isposition of rights" in inventions made pursuant to federally funded research contracts. 35 U.S.C. 202 (title). The statute comprehensively addresses the rights of the federal government, university contractor, and individual inventor. Where, as here, a university elects to exercise its right under Bayh-Dole to retain title to an invention, the individual inventor cannot assign that invention to a third party because the invention is assigned, by operation of law, to the university.

A. Federal Law Has Long Disposed Of Ownership To Federally Funded Inventions By Operation Of Law

For at least 60 years—30 years before Bayh-Dole was enacted—the federal government has, through various statutory and regulatory means, denied inventors the right to assign federally funded inventions to third parties. Those Bayh-Dole predecessors make clear that federal law may, and often does, provide for disposition of federally funded inventions by operation of law. An inventor's purported assignment of a federally funded invention to a third party is therefore ineffective to the extent it is inconsistent with superior rights of the federal government or federally funded contractor.

1. Executive Order 10096 and numerous statutes provide for federal ownership of federally funded inventions

Roche's contention that there is a background principle allowing inventors freely to assign federally funded inventions has not been accurate for at least 60 years. In 1950, President Truman issued Executive Order 10096 to establish "a uniform patent policy for the Government with respect to inventions made by Government employees." 35 U.S.C. 207 (note) (reproduced in an appendix hereto). The Order provides that when an invention is "made in consequence of the official duties of the inventor" the federal government "*shall obtain* the entire right, title, and interest" in the invention. App., *infra*, 1a (emphasis added). When the government decides not to "require[] assignment to" itself, it will nevertheless "reserv[e]" to itself a nonexclusive license. *Id.* at 1a-2a.

Beginning no later than 1954, in numerous statutes, Congress has likewise allocated to the federal government ownership of contractors' inventions made with federal funding. In the Atomic Energy Act of 1954, P.L. 83-703, § 152, 68 Stat. 944, Congress specifically provided that "[a]ny invention or discovery" conceived in the course of a contract with the Atomic Energy Commission "*shall be deemed to have been made or conceived by the Commission,*" thereby "*entitling the Commission to take title to*" the resulting patent unless it "waive[s] its claim." *Ibid.* (emphasis added); see also P.L. 87-206, § 10, 75 Stat. 477 (amending AEA to affirm that such inventions "*shall be vested in, and be the property of,* the Commission") (codified at 42 U.S.C. 2182) (emphasis added); National Aeronautics and Space Act of 1958, P.L. 85-568, § 305, 72 Stat. 435 (NASA-funded inventions "shall be the exclusive property of the United States") (codified at 42 U.S.C. 2457(a)).

Executive Order 10096 and agency-specific vesting statutes were, moreover, fresh in the mind of the legislators who enacted Bayh-Dole in 1980. A Government Accounting Office report submitted to Senator Bayh in connection with Bayh-Dole's consideration noted that rights to inventions made by NASA employees are "determined by the agency pursuant to provision of Executive Order 10096" and that, under NASA's statute, "any invention conceived or first reduced to practice in the performance of work under a NASA contract becomes the exclusive property of the Government." *Science and Technology Research and Development Utilization Policy Act: Hearing Before the Subcomm. On Science, Technology, and Space,* 96th Cong. 211 (1979) (reprinting letter from Comptroller General).

Also, in the immediately preceding years, Congress had adopted several additional statutes specifying that "title to such [federally funded] invention shall vest in the United States, and if patents on such invention are issued they shall be issued to the United States." Federal Nonnuclear Energy Research and Development Act of 1974, P.L. 93-577, § 9, 88 Stat. 1887 (FNRDA) (codified at 42 U.S.C. 5908(a)). See also 42 U.S.C. 6981(c)(3) (1976) (incorporating FNRDA); 7 U.S.C. 178j (Supp. II 1979) (same); 42 U.S.C. 5585(b) (Supp. II 1979) (same); 42 U.S.C. 7879 (Supp. II 1979) (same), *repealed by* Water Resources Research Act of 1984, P.L. 98-242, §§ 109-110(a), 98 Stat. 97, 101 (codified at 42 U.S.C. 10308). Indeed, Congress specifically referenced these statutes in Bayh-Dole. 35 U.S.C. 210(a).

Thus, it is clear that, by the time of Bayh-Dole's enactment, there was no established presumption that researchers who make inventions with federal funding retain a "freedom to assign" those inventions to third parties.

2. *Numerous courts have recognized that the government obtains title pursuant to Executive Order 10096 and agency-specific vesting statutes by operation of law*

As several courts have recognized, when the government obtains rights in a federal employee's invention pursuant to Executive Order 10096, the employee is deemed to have "assigned title and all other rights to such discover[y]" to the government *"by operation of law."* *Li* v. *Montgomery*, No. 99-5106, 2000 WL 815992, at *2 (D.C. Cir. May 15, 2000) (emphasis added). Even if the employee has not executed an assignment of title to the government, the government is nonetheless "the

owner of the" invention. *Heinemann* v. *United States*, 796 F.2d 451, 456 (Fed. Cir. 1986), cert. denied, 480 U.S. 930 (1987). In *Heinemann*, the Federal Circuit affirmed dismissal of a government-employee inventor's patent infringement suit, even though the inventor's formal assignment to the government was deemed invalid, because the invention "became the property of the Government," not the inventor, under the Executive Order. *Ibid.*

Similarly, it is clear that under the agency-specific vesting statutes, an inventor is unable to assign rights in a federally funded invention to a third party without the United States' consent. As the Federal Circuit recognized in a case involving a pre-Bayh-Dole funding agreement, these agency-specific statutes "clearly provide[] that title to any invention made or conceived under a [covered] contract 'shall vest' in the United States." *FilmTech Corp.* v. *Hydranautics*, 982 F.2d 1546, 1550 (Fed. Cir. 1992), cert. denied, 510 U.S. 824 (1993) (construing FNRDA (as incorporated by the Saline Water Conversion Act, 42 U.S.C. 1959d note (1976) (repealed 1978))). Thus, the court held, the inventor's purported assignee lacked standing to sue on the patent because the inventor "had no right to assign it." *Id.* at 1553. Rather, title had "automatically vested in the United States" by "operation of law." *Ibid.*

Moreover, under these authorities, the government may apply for a patent as owner of the invention, even if the inventor refuses to sign an assignment in favor of the government. When an inventor "refus[es]" to "execute an assignment to the Government," the government may apply for the patent without the signed documents. *Boutros* v. *Boutros*, 231 U.S.P.Q. 829, 830 (Com'r Pat. & Trademarks July 10, 1986). By operation

of law, "the Government is considered to be the owner" of the invention. *Id.* at 830-831. See 37 C.F.R. 1.47(b) (allowing "person to whom an inventor has assigned or agreed in writing to assign the invention, *or who otherwise shows sufficient proprietary interest*" to apply for patent despite "the inventor['s] refus[al] to execute an application for patent") (emphasis added).

3. NSF and NIH regulations also restricted an inventor's ability to assign federally funded inventions to third parties

The regulatory programs put in place by the National Science Foundation (NSF) and NIH—then part of the Department of Health, Education, and Welfare (HEW)—before Bayh-Dole's enactment also made clear that federally funded researchers were not "free to assign" federally funded inventions to third parties. Although NIH and NSF adopted policies that favored leaving title to federally funded inventions in universities and similar nonprofit institutions, those policies did not leave to individual inventors the option to assign their federally funded inventions to third parties.

NSF's generally applicable regulations were similar to Executive Order 10096. The regulations provided that NSF would "determine the disposition of the invention [made under the grant] and title to and rights under any patent application." 45 C.F.R. 650.4(b) (1977). The university was required to agree "for itself *and for its employees*" that "all documents will be executed and all other actions taken necessary or proper to carry out the determination of the Foundation." *Ibid.* (emphasis added). Thus, as with Executive Order 10096, if NSF determined that title to an NSF-funded invention should belong to the government, the indi-

vidual inventor was not free to assign the invention to a third party, but was instead obligated to execute the documents necessary to permit NSF to apply for a patent. Only if neither the government nor the university wished to take title could the individual inventor apply to retain rights, 45 C.F.R. 650.9(c)(4), and even then the inventor took ownership subject to a "reserv[ation]" of minimum rights to the government, 45 C.F.R. 650.9(c)(4), 650.10 (1977).

HEW's generally applicable regulations were similar to NSF's. They also provided that "disposition of all rights in and to" inventions made under research grants "shall be subject to determination" by the agency, which had the authority to "require that all domestic rights in the invention shall be assigned to the United States." 45 C.F.R. 8.1(a), 8.2(d) (1977).

As under the Executive Order and agency-specific vesting statutes, an inventor could not effectively assign his federally funded invention to a third party inconsistent with the disposition of rights provided by the applicable legal framework. In *VDI Technologies, Inc.* v. *Price*, No. Civ. 90-341, 1994 WL 485778 (D.N.H. Aug. 31, 1994), the court held that the inventors' purported assignment to a subcontractor of an invention made under an HEW contract failed to convey "enforceable title" to the patent because HEW was entitled to ownership under its pre-Bayh-Dole regulations. *Id.* at *1. The court reasoned that HEW's regulations "automatically vest[ed] in the government the exclusive right to determine who could obtain and exercise ownership rights and on what terms." *Id.* at *4. It did not matter that the subcontractor had received an assignment from the inventors because their "*interest ... was necessarily circumscribed by the regulations reserving*

to the government the right to determine ownership of the invention." Id. at *6 (emphasis added).

Beginning in the late 1960s and lasting until the late 1970s, when the Carter administration reverted to a policy of government ownership, see S. Rep. No. 96-480, at 21 (1979) ("Senate Report"), both NSF and NIH adopted a policy that favored allowing nonprofit institutions to retain ownership of federally funded inventions. 45 C.F.R. 650.8(a) (1977); 45 C.F.R. 8.6(b) (1977). To qualify for an NSF Institutional Patent Agreement (IPA), nonprofit institutions were asked to "give assurance that employees are legally obligated to assign to the institution any inventions made by them in the course of or under awards." 45 C.F.R. 650.8(b)(2) (1977). NIH's IPAs similarly required that a university's employees assign to the university all inventions made under the NIH grant. See Federal Council for Science and Technology, *Report on Government Patent Policy* 330-331 (1976). And, as with the agencies' generally applicable regulations, NSF's and NIH's IPAs "reserve[d] to the Government" important rights. 45 C.F.R. 650.8(c)(1) (1977) (incorporating Section 650.10); 45 C.F.R. 8.3 (1977).

As the above demonstrates, while NSF's and NIH's precise policies regarding disposition of rights in federally funded inventions differed from those of Executive Order 10096 and the agency-specific vesting statutes, NSF's and NIH's regulations preserved the rights and interests of the public in the fruits of research conducted at public expense. Under none of these frameworks was an individual inventor "free to assign" his rights in a federally funded invention to a third party.

4. The courts have upheld the government's authority to dispose of federally funded patents by operation of law against challenges based on inventors' "freedom to assign"

By the time of Bayh-Dole's enactment, Executive Order 10096 had already been upheld against challenge by an inventor arguing, as Roche does here, that inventors are necessarily free to dispose of their federally funded inventions as they see fit. In *Kaplan* v. *Corcoran*, 545 F.2d 1073 (1976), the Seventh Circuit considered and rejected an argument that the Executive Order violated the Patent Clause of the Constitution, Art. I, § 8, cl. 8, *id.* at 1075-1077.

In *Kaplan*, the inventor argued, on the basis of *United States* v. *Dubilier Condenser Corp.*, 289 U.S. 178 (1933), that the President lacked authority to compel transfer to the government of an invention made in the course of federal employment. The Seventh Circuit observed that, contrary to the inventor's contentions, *Dubilier* did not question whether federal law *could* trump an inventor's freedom to assign federally funded inventions. Rather, *Dubilier* had expressed the view that "formulation" of a policy concerning government ownership of federal employees' inventions "belongs solely to Congress," rather than the courts or an "unspecified" administrative officer. *Kaplan*, 545 F.2d at 1076 & n.2 (quoting *Dubilier*, 289 U.S. at 208-209). The court of appeals upheld Executive Order 10096 on the ground that Congress had given the President broad authority to promulgate regulations concerning federal employees and federal property. *Id.* at 1077 (citing 5 U.S.C. 301). Moreover, by the time of the *Kaplan* decision in 1976, Congress had, at the very least, acquiesced

in the Executive's longstanding policy of taking ownership of inventions made in the course of federal employment. *Ibid.* The Federal Circuit has endorsed *Kaplan*'s reasoning and likewise rejected a challenge to the Executive Order as unconstitutionally depriving federally funded inventors of property. See *Heinemann*, 796 F.2d at 455.

Courts have similarly upheld the constitutionality of the analogous "work-for-hire" doctrine of the Copyright Act of 1976, which provides that when "a work [is] prepared by an employee within the scope of his or her employment," "the employer ... is considered the author" of the work and owner of the copyright. See *Community for Creative Non-Violence* v. *Reid*, 490 U.S. 730, 737-738 (1989) (quoting 17 U.S.C. 101(1), 201(b)). This Court applied the doctrine in *Reid* without suggesting any doubt as to its constitutionality, *ibid.*, and the Second Circuit—the only court of appeals to consider a constitutional challenge to the doctrine—dismissed the challenge out of hand, *Childress* v. *Taylor*, 945 F.2d 500, 506-507 n.5 (2d Cir. 1991).

Congress's authority to protect copyrights derives from the same constitutional provision that grants Congress authority to protect patents. See U.S. Const. Art. I, § 8, cl. 8. Therefore, just as Congress can assign ownership of a copyright to a writer's employer, it can also assign ownership of a patent to an inventor's employer or to the government that funded the invention.

B. Like The Statutes And Regulations That Preceded It, Bayh-Dole Controls Disposition Of Title To Federally Funded Inventions In Order To Promote The Public Interest

Bayh-Dole was adopted in order to establish a uniform national policy regarding ownership of inventions made by nonprofits or small businesses with funding from the federal government. Although Bayh-Dole's policy of allocating title to nonprofits or small businesses differs from the policy of federal ownership reflected in Executive Order 10096 and agency-specific vesting statutes, Bayh-Dole, like those predecessors, also provides for a "[d]isposition of rights" in federally funded inventions by operation of law. 35 U.S.C. 202 (title). There is no reason to believe, as Roche contends, that Congress would leave Bayh-Dole's important public policy objectives, affecting hundreds of billions of dollars in federal research funding, to be frustrated by individual inventors who assign their inventions to third parties.

1. Although Roche may argue that Bayh-Dole is different from the Executive Order and other statutes precisely because it allocates rights to the nonprofit or small business rather than to the federal government itself, that would not be correct. Bayh-Dole reserves to the federal government important rights that could be defeated if individual inventors were free to assign their inventions inconsistent with Bayh-Dole's framework.

Significantly, Bayh-Dole specifically permits the funding agency, in certain circumstances, to take full ownership of the invention. Section 202 creates a "right[] of the Government," 35 U.S.C. 202(b), to "eli-

minat[e]" the nonprofit's "right to retain title" (1) when, in "exceptional circumstances," Bayh-Dole's policies would be better promoted by greater government rights, (2) when the invention implicates the security of "foreign intelligence or counter-intelligence activities," (3) when the invention concerns "nuclear propulsion or weapons related programs," or (4) when the nonprofit is "subject to the control of a foreign government." 35 U.S.C. 202(a), (b). If, as Roche contends, Bayh-Dole "does not regulate" an inventor's "freedom to assign" federally funded inventions, the funding agency's determination to assert direct ownership under Section 202(b) can be defeated by the inventor assigning the invention to a third party. Nothing in Bayh-Dole would support a conclusion that the federal government's assertion of rights in such sensitive areas as foreign intelligence and nuclear weapons could be unilaterally circumvented by the inventor.

2. Even when the funding agency does not invoke the Section 202(a) exceptions, Bayh-Dole reserves important rights to the federal government that would be frustrated if individual inventors were "free to assign" their inventions outside the Bayh-Dole framework. Bayh-Dole provides that "the Federal Government may receive title to any subject invention" if it is not timely disclosed or if the contractor does not timely elect to retain rights or does not timely file a patent application. 35 U.S.C. 202(c)(1)-(3). The Act also grants the federal agency "a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced" the invention for governmental purposes. 35 U.S.C. 202(c)(4). Moreover, if the contractor fails to take "effective steps to achieve practical application," to adequately "alleviate health or safety needs," or to

require exclusive licensees to manufacture substantially in the United States, the federal government has "the right" to require the contractor or its licensee to grant a license to another responsible applicant. 35 U.S.C. 203(a). These governmental "rights" apply to inventions in which a "small business firm or nonprofit organization has acquired title under this chapter." *Ibid.* If an inventor were "free to assign" the invention to a third party outside the Bayh-Dole framework, none of these governmental rights in furtherance of the public interest would apply vis-à-vis the third party, which would not have "acquired title under" Bayh-Dole. *Ibid.*

3. Roche's argument that inventors are "free to assign" federally funded inventions is also contrary to the Bayh-Dole provision that expressly addresses inventor rights. Section 202(d) specifies that an inventor can exercise ownership rights in the invention only if two circumstances are met: (1) the contractor does not exercise its superior right to take title; and (2) the federal agency affirmatively grants a request by the inventor. 35 U.S.C. 202(d); see *Fenn* v. *Yale Univ.*, 184 Fed. Appx. 21, 22 (2d Cir. 2006) (summary order). Moreover, even when permitted to take title, the inventor does so "subject to the provisions of this Act and regulations promulgated hereunder." 35 U.S.C. 202(d). These regulations "impose" requirements upon the inventor that are similar to those imposed upon contractors that take title. 37 C.F.R. 401.9, 401.14(a) (standard clause ¶¶ (d)(1), (d)(3), (i), (j)). It is impossible for the federal government to "impose" these restrictions on an inventor's patent rights if, as Roche contends, "the Act does not regulate" the inventor, but only "relationships of ... nonprofit grantees with the Government." Roche Supp. Pet. Br. 11-12 & n.6.

4. The relationship between Bayh-Dole and the agency-specific vesting statutes discussed above further supports the conclusion that Bayh-Dole allocates ownership of federally funded inventions by operation of law. Congress was clearly aware of its authority to dispose of rights in federally funded inventions by operation of law because Bayh-Dole expressly "take[s] precedence over any other Act which would require a disposition of rights in subject inventions" different from Bayh-Dole, and specifically takes precedence over identified vesting statutes that otherwise dictate the disposition of title to government funded inventions. 35 U.S.C. 210(a) (listing 7 U.S.C. 178j; 42 U.S.C. 2182, 2457, 5585(b), 5908, 6981(e), 7879 as among the statutes displaced). Significantly, however, Bayh-Dole does not displace the vesting statutes with respect to large, for-profit contractors. 35 U.S.C. 210(b). Therefore, if Roche's reading of Bayh-Dole were correct, only the employees of non-profit and small-business contractors would be free to assign away the government's statutory rights, whereas employees of large, for-profit contractors could not. See *Hydranautics*, 982 F.2d at 1548, 1553-1554.[2] Nothing in Bayh-Dole suggests that Congress intended to create such a discrepancy.

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[2] Agencies apply Bayh-Dole's policy favoring contractor ownership to large, for-profits in exercising their waiver authority under the agencies' individual vesting statutes. See E.O. No. 12591, 52 Fed. Reg. 13,414 (Apr. 10, 1987); Memorandum on Government Patent Policy, Pub. Papers 248 (Feb. 18, 1983). Such disposition of rights pursuant to statutory authority under the vesting statutes could not be frustrated by an inventor's contrary assignment. Cf. *Hydranautics*, 982 F.2d at 1548, 1553-1554.

II. BAYH-DOLE DOES NOT "CONFISCATE" PRIVATE INVENTIONS, AND ROCHE'S CLAIM THAT THESE PATENTS WERE INVENTED BY CETUS IS CONTRARY TO THE FEDERAL CIRCUIT'S PREMISE

This case comes to the Court on the premise that Stanford has a validly patented invention conceived and reduced to practice by Stanford inventors with federal funding *after* Holodniy left Cetus. Pet. App. 5a-6a, 15a. Amici express no opinion whether Stanford will be able to sustain that contention on remand. The premise is important, however, because it demonstrates that the issue before the Court concerns not the outer limits of the Bayh-Dole framework, but its core. Contrary to Roche's suggestion, the Federal Circuit did not award Roche an equitable "*share*[]" of the patents in recognition of Cetus's "major contributions" to the invention. Roche Supp. Pet. Br. 11. Rather, the Federal Circuit adopted a categorical rule that would allow a university inventor to assign the *entirety* of *any* federally funded invention to *any* third party, even one with no connection to the invention.

Contrary to Roche's contentions, giving effect to Bayh-Dole's disposition of rights when a university researcher makes an invention in the course of a federally funded project does not confiscate the inventions of private companies. Bayh-Dole only reaches inventions made by government contractors pursuant to federal research funding. It is Roche's argument, not Stanford's, that threatens to chill future collaboration between universities and industry by raising the prospect that the product of their cooperation will be assigned to a third party.

A. The Federal Circuit's Decision Does Not Rely On Cetus's Purported Contribution To The Patents But On A Broad Legal Holding That University Inventors Are Free To Assign Inventions Conceived And Reduced To Practice Using Federal Funds

1. Cetus's contribution to the discovery was published in 1991 and could not form the basis for Stanford's patented inventions

Roche contends that construing Bayh-Dole to preclude inventors from assigning federally funded inventions to third parties would result in "confiscat[ing] intellectual property rights from non-funded entities whose private resources and expertise lead to the conception of inventions." Roche Supp. Pet. Br. 2. In its petition-stage briefs, Roche attempted to rewrite the Federal Circuit's opinion, characterizing it as holding that "[t]he invention was conceived and the assay completed at Cetus *before* Stanford performed any work using federal funds." Roche Supp. Pet. Br. 3 (citing Pet. App. 14a). That assertion mischaracterizes the court of appeals' decision. To the contrary, the Federal Circuit declined to decide precisely how long before Stanford's May 1992 patent application the inventions were "conceived." Pet. App. 14a. Instead, the court of appeals held that Cetus owned Holodniy's patent rights "*[e]ven if* Holodniy conceived and reduced to practice [the inventions] *after departing Cetus*." *Id.* at 15a (emphasis added). Likewise, the Federal Circuit assumed that the inventions were federally funded under a grant from NIH. Pet. App. 5a-6a, 18a-21a.

Stanford's appeal from the district court's finding of obviousness rests on the premise that the patented

inventions were conceived and reduced to practice *after* publication of an April 1991 article in the *Journal of Infectious Diseases* (JID) that reported the results of Holodniy's collaboration with Cetus researchers. See Pet. App. 38a-39a. Holodniy and his Cetus collaborators published the JID article without filing a patent application on the results of their work. *Ibid.* The district court held that the inventions claimed by Stanford were obvious in light of what was already publicly known through the 1991 JID article. 563 F. Supp. 2d 1016, 1016, 1023-24, 1027-28, 1043 (N.D. Cal. 2008). Stanford's appeal of that holding contends that the patented inventions reflected novel and non-obvious work performed at Stanford by Stanford researchers after publication of the JID article. See Stanford C.A. Br. 6-26. The Federal Circuit did not reach the merits of the obviousness issue. Instead, the court of appeals held that Stanford lacked standing to enforce the patents because Holodniy had, by signing the Visitor Confidentiality Agreement (VCA), assigned his future inventions to Cetus, including inventions made at Stanford with federal funding. See Pet. App. 12a-15a, 28a.

Thus, as the case comes to this Court, it presents the question whether Holodniy's purported assignment of his future inventions could be effective as to a future invention both conceived and reduced to practice at Stanford while Holodniy was working under federal funding, notwithstanding Stanford's assertion of its right under Bayh-Dole to retain title. In other words, this case lies at the very heart of federally funded research to which Bayh-Dole is addressed.

2. The Federal Circuit did not give Cetus a "share" of the inventions to reward Cetus's "contribution," but rather adopted a broad ruling that university inventors can freely assign federally funded inventions

Roche contended throughout its petition-stage briefs that the Federal Circuit's holding merely recognized Roche's right to "*share*[]" title in light of "major contributions" that Cetus made to the invention. Roche Supp. Pet. Br. 11. See also *id.* at 13; Br. in Opp. 12-13, 19-20. To the contrary, the Federal Circuit adopted a categorical rule that researchers are free to assign their federally funded inventions to third parties—without consideration of equities. Under the Federal Circuit's rule, if Holodniy had been the sole inventor, he would have been free to assign his invention to any third party of his choosing, including one with no connection to the invention.

That Roche receives only a "share" of the patents is due only to the fortuity that Holodniy was one of multiple Stanford inventors, and the other researchers did not assign their rights to Cetus or another third party. The rule advocated by Roche does not apply only to Holodniy or only to assignment by one of multiple co-inventors. Rather, on Roche's view, each inventor had the "statutory right to assign his interest in [the] patents" as he saw fit. Br. in Opp. 18. If each of the co-inventors had assigned his rights to a third party, or if Holodniy had been the sole inventor, Stanford (and consequently the federal government) would have been left with no interest whatsoever in the federally funded invention. The fact that "Stanford remains a co-owner of the patents-in-suit" based on assignment from Holodniy's co-inventors, Br. in Opp. 11, is mere happens-

tance that is entirely irrelevant to the legal question presented in the case.

Roche's repeated references to the fact that the inventions built upon work that Holodniy had done at Cetus, Br. in Opp. 3-6, 20, 24, is also a red herring. The fact that the inventions built on Holodniy's work at Cetus was relevant to the assignment issue only because the VCA purported to assign all future inventions made "as a consequence of [Holodniy's] access to CETUS' facilities or information." Pet. App. 123a. But the Federal Circuit's holding, as Roche elsewhere acknowledges, does not require that the inventor's assignee have a connection to the invention. Rather, under the Federal Circuit's broad ruling that an inventor has a "statutory right to assign his interest," Br. in Opp. 18, Holodniy could have assigned his rights in these federally funded inventions in satisfaction of a personal debt or for any other reason.

Roche's arguments sound in *quantum meruit*—that Roche should be rewarded for the value of Cetus's contributions. But that is not the rule under review by this Court.

B. Bayh-Dole Does Not Interfere With Rights Of Industry Collaborators

Despite Roche's hyperbolic contentions, the position advocated by Stanford and the United States would not "confiscate" the intellectual property of industry collaborators. To the contrary, Bayh-Dole respects the rights of industry collaborators who are not federally funded. For 30 years, research institutions and private enterprises have entered into mutually agreeable contractual arrangements regarding their cooperative research endeavors. It is Roche's argu-

ment, not Stanford's, that threatens to hamper continued research collaboration.

1. Bayh-Dole applies only to "subject inventions." 35 U.S.C. 201(e). In order to qualify as a "subject invention," the invention must first be an "invention of the contractor" and, further, it must be "conceived or first actually reduced to practice in the performance of work under a funding agreement." *Ibid.* To qualify as an "invention of the contractor," it must be an "invention or discovery [of the contractor] which is or may be patentable" under the Patent Act. 35 U.S.C. 201(d). Thus, Bayh-Dole does not apply to Cetus's inventions. This case, however, is premised on the assumption that the inventions were the discoveries of Stanford researchers acting under an NIH grant—the very core of activity that Bayh-Dole addresses.

Similarly, if, as Roche implies, Br. in Opp. 5-6, Cetus employees were co-inventors, Bayh-Dole would not govern disposition of the Cetus co-inventors' interest in the invention. In Section 202(e), Bayh-Dole addresses the circumstance when university employees and government employees are co-inventors and recognizes that Bayh-Dole would not govern the disposition of rights arising from the federal employees' co-inventorship. 35 U.S.C. 202(e) (noting that federal agency could assign rights that it acquires pursuant to E.O. 10096 to the nonprofit "for the purpose of consolidating rights in the invention"). Although the statute does not specifically address the situation when the co-inventor is employed by a private entity using private funding, subsection (e) strongly suggests that only the rights of those co-inventors conducting research under a federal funding agreement are governed by Bayh-Dole. Again, no question of private co-inventors is pre-

sented here because all the co-inventors were Stanford researchers acting under federal funding. See Pet. App. 15a, 18a-21a.

2. The fact that Bayh-Dole governs disposition of inventions made by nonprofits with federal funding has not, contrary to Roche's assertions, "discourage[d] scientific cooperation" between universities and commercial concerns. Roche Supp. Br. 13-14. Rather, it is Roche's theory of university researchers as free agents, able to assign federally funded inventions to third parties, that threatens this cooperation.

For 30 years, universities have routinely entered into sponsored research agreements with private industry with the understanding that, if federal funding is also involved, the inventions of university researchers will be governed by the terms of Bayh-Dole. Some agreements may specify the terms of a license that the industry collaborator will receive regarding any inventions; some simply indicate that industry sponsors will have the first right to negotiate a license. All of these agreements, however, start with the premise that the university will have the right under Bayh-Dole to retain title to federally funded inventions and will be in a position to license the inventions back to the private entity that helped sponsor the research. Roche's argument threatens the foundation of that collaboration by raising the prospect that individual university researchers could assign resulting inventions to yet another third party, thereby depriving both the university *and* the private sponsor of the benefit of their collaboration.

The Engineering Research Centers (ERCs) organized at numerous universities under the auspices of

NSF to support targeted research are examples of how such industry and university collaboration can be organized. See, *e.g.*, Engineering Research Centers: Linking Discovery to Innovation, http://www.erc-assoc.org/factsheets/ERC%20Overview%20Fact%20Sheet_09-final.pdf (last visited Dec. 23, 2010). In many instances, sponsoring companies become members of an ERC, and members are entitled to preferential access to discoveries and to negotiate licensing terms. Although these collaborations have proceeded smoothly, on the assumption that the university can retain title to the inventions of university researchers, Roche's arguments raise the prospect that university researchers would be free to assign ERC inventions to members' competitors who had not participated in sponsoring the ERC's work. Faced with such a risk, corporations might well choose not to participate as members in future ERCs.

The facts of this case provide examples both of how collaborative research *should* and *should not* be conducted. In February 1989, Cetus negotiated with Stanford a Materials Transfer Agreement (MTA) that set forth the terms of their collaboration. Pet. App. 33a-34a. Under the terms of the MTA, Cetus agreed to "provide Stanford with 'certain research substances and know-how' in exchange for certain concessions on the part of Stanford," including "the first option to an exclusive license, at a reasonable royalty to be negotiated in good faith ..., or at CETUS' option, a nonexclusive license." *Ibid.* (quoting MTA). Roche asserted a license under the MTA, but the district court rejected that defense because Stanford had not consented to assignment of the license from Cetus to Roche. *Id.* at 70a-72a. As the MTA reflects, Cetus was in a position

to negotiate the rights it would obtain in return for its contribution to Stanford's invention, but Cetus failed to negotiate a license that could be assigned to Roche. Roche's complaint thus lies with Cetus's negotiators, not Bayh-Dole.

Instead of relying on the MTA—which Cetus negotiated openly *with Stanford*, but which did not convey rights that Cetus could assign to Roche—Roche relies on a VCA, signed by Holodniy without actual notice to Stanford. See Pet. App. 16a (holding only that Stanford had "inquiry notice of the VCA"). In the VCA, Holodniy purportedly assigned away all future inventions he might conceive as a "consequence" of what he learned at Cetus. *Id.* at 4a. In other words, Cetus specifically set out to obtain for itself exclusive ownership of any inventions that Holodniy made at Stanford after he left Cetus, as long as Holodniy's experience at Cetus contributed to his ability to make the invention.

If agreements like the VCA were sufficient to defeat universities' Bayh-Dole rights, universities could not afford to permit their researchers to visit other research facilities and would naturally be reluctant to hire researchers who had worked for employers who used such forms. Cf. *Guth* v. *Minnesota Mining & Mfg. Co.*, 72 F.2d 385, 388-389 (7th Cir. 1934), cert. denied, 294 U.S. 711 (1935) (patent assignment contract unlimited in time and subject matter was unenforceable because it would prevent moving to new employment). Thus, it is Roche's argument that, if accepted, would discourage continued collaboration between universities and private industry.

III. The Federal Circuit's Decision Undermines The Certainty Of Title That Is Fundamental To Bayh-Dole's Commercialization Objectives

Congress enacted Bayh-Dole to encourage collaboration between universities and private enterprise in commercializing inventions arising from federally funded research. Bayh-Dole has spurred the commercialization of thousands of inventions and contributed hundreds of billions of dollars to the economy. The court of appeals' decision raises questions whether inventions believed to be owned by the university may, in fact, be owned by another party. The inevitable result of this uncertainty is that some university inventions will not be licensed, and some beneficial products will never be developed.

A. Prior To Bayh-Dole, Lack Of Certainty Regarding Universities' Ability To Own And License Federally Funded Inventions Impeded Their Successful Commercialization

Before Bayh-Dole, government contractors' rights to inventions resulting from federally funded research were governed by a convoluted and often contradictory assortment of 26 different federal agency policies. U.S. Gov't Accountability Office, GAO-09-742, *Information on the Government's Right to Assert Ownership Control over Federally Funded Inventions* 4 (2009) ("GAO Report"); H.R. Rep. No. 96-1307, pt. 1, at 3 (1980) ("House Report"); Senate Report 2-3. This "potpourri" of policies "confus[ed] and discourage[d]" contractors, Bradley Graham, *Patent Bill Seeks Shift to Bolster Innovation*, Wash. Post, Apr. 8, 1979, at M1 - especially universities and small businesses, which lacked large

legal staffs to negotiate this "policy maze," Senate Report 2-3.

Agency policies generally provided that the government would take title to patents arising from federally funded research unless the agency waived its rights. Senate Report 2. Government agencies proved ineffective at bringing the inventions they owned to market. Government agencies owned between 25,000 and 30,000 patents, but less than approximately 4% to 5% of them were developed commercially. Graham, *supra*, M2; GAO Report 2. In order for a university to obtain ownership of a federally funded invention, it generally had to wait until the invention was identified and then petition the funding agency for a waiver. Senate Report 2, 21, 30. Waiver proceedings were lengthy, often a year or more, and extremely burdensome on both agencies and contractors. *Ibid.* Because universities and other government contractors had no certainty that they would obtain title to inventions resulting from federally funded research, they were unable to attract private companies as licensees willing to provide essential funding and assistance in bringing new discoveries to market. See *id.* at 21, 30; H.R. Con. Res. 328, 11th Cong. 2-3 (2010) ("2010 House Resolution").

In the late 1960s and early 1970s, HEW and NSF sought to spur innovation by implementing IPA programs under which universities were given a first option to own and manage inventions resulting from agency-funded research. Senate Report 21; Howard Bremer, Joseph Allen, & Norman J. Latker, *The Bayh-Dole Act and Revisionism Redux*, 78 Pat., Trademark & Copyright J. 483, 485 (Aug. 14, 2009). While these programs achieved some commercialization, see Senate Report 21, they ultimately failed to give universities

the certainty necessary to fully realize the potential of federally funded research. Contractors were still forced to navigate a convoluted web of confusing and often conflicting agency policies. House Report 3. And the Carter administration's termination of HEW's IPA program in 1978 demonstrated that any given IPA program could be "changed at the whim of a political appointee." Bremer, *supra* at 487.

B. By Providing Universities Clear Title, Bayh-Dole Has Been Enormously Successful In Encouraging Commercialization Of Federally Funded Inventions

In what has been described as one of the most inspired legislative acts in American history, *Innovation's Golden Goose*, The Economist, Dec. 14, 2002, at 3, Congress enacted Bayh-Dole in 1980 to "end this uncertainty" surrounding ownership of federally funded patents "and prevent these promising inventions from being suffocated under reams of unnecessary bureaucratic redtape." Senate Report 21. Recognizing that universities and nonprofit organizations had shown themselves to be "much more efficient in delivering these important discoveries to the marketplace than are [government] agencies," *id.* at 29, Congress amended the Patent Act to "automatically grant" nonprofit government contractors "title to inventions arising from Government-supported research," *id.* at 36 (reprinting Congressional Budget Office letter).

Bayh-Dole has been incredibly successful in stimulating innovation by giving universities certainty regarding their ownership of federally funded inventions. Whereas approximately 250 patents were issued to universities in 1980, with only a small percentage of

them resulting in commercial products, universities received over 3,000 patents and executed over 5,000 licenses and options in 2008. BayhDole25, Inc., *The Bayh-Dole Act at 25* 23 (2006); Press Release, Ass'n of Univ. Tech. Managers, *New Survey Reveals Universities' Impact on the U.S. Economy* (Feb. 2010). Universities helped bring to market 4,338 new products between 1998 and 2006, or more than 1 new product every day. *The Role of Federally Funded University Research in the Patent System: Hearing Before the S. Comm. on the Judiciary*, 110th Cong. 118 (2007) (statement of Charles F. Louis, Vice Chancellor for Research, University of California, Riverside). Examples of new products arising from university research include:

- Internet Explorer® (Mosaic) and Eudora Email (U. of Illinois)
- Google® (Stanford)
- Haemophilus B conjugate vaccine (U. of Rochester)
- Osteoporosis treatment (U. of Washington)
- Psoriasis treatment (Harvard)
- LYRICA® for fibromyalgia (Northwestern U.)
- TRUSOPT® opthalmic drops used for glaucoma (U. of Florida).[3]

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[3] Ass'n of Univ. Tech. Managers, *Technology Transfer Stories: 25 Innovations That Changed the World* 40-42, 94-96, 106-08 (2006); Council on Governmental Relations, *The Bayh-Dole Act: A Guide to the Law and Implementing Regulations* 8 (1999); Press Release, Ass'n of Univ. Tech. Managers, *supra*; Arundeep S. Pradhan, Op-Ed, *Defending the University Tech Transfer System*, Business Week, Feb. 19, 2010; Jo Thomas, *Satisfaction in Job Well Done Is Only Reward for E-Mail Software Inventor*, N.Y. Times,

Bayh-Dole has also made an extraordinary contribution to the national economy. Just last month, Congress recognized that the "economic activity spurred on by the Bayh-Dole Act include[s] the formation of more than 6,500 new companies from the inventions created under the Act, an estimated contribution of $450,000,000,000 to United States gross industrial output, and the creation of 280,000 new high technology jobs between 1999 and 2007." 2010 House Resolution 4; see also David Roessner *et al.*, *The Economic Impact of Licensed Commercialized Inventions Originating in University Research, 1996-2007* 7-8 (2009), *available at* http://www.bio.org/ip/techtransfer/BIO_final_report_9_3_09_rev_2.pdf. Bayh-Dole has also led to "the creation and dominance of the United States biotechnology and information technology industries." 2010 House Resolution 3.

C. The Federal Circuit's Decision Undermines The Certainty Of University Title That Is Central To Bayh-Dole's Success

By making ownership of federally funded inventions turn not on Bayh-Dole, but on contracts that individual researchers might have signed decades ago without noticing or understanding the potential impact and perhaps without even retaining a copy, the court of appeals re-injects uncertainty into the commercializa-

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Jan. 21, 1997, at A10; Sharita Forrest, *NCSA Web Browser 'Mosaic' Was Catalyst for Internet Growth*, Inside Illinois (Apr. 17, 2003), *available at* http://news.illinois.edu/11/03/0417/index.html; Press Release, Nw. Univ., http://www.northwestern.edu/newscenter/stories/2007/12/lyrica.html (last visited Dec. 23, 2010).

tion of federally funded inventions, with an attendant waste of federal research dollars.

1. The court of appeals' decision casts doubt on university title

Under the rule adopted by the Federal Circuit, university ownership of federally funded inventions turns on judicial construction of dueling assignments executed years before the invention. The court concluded that Stanford's "agree to assign" language creates only a promise to assign rights in the future whereas the VCA's "hereby assign" language immediately granted Cetus a right in Holodniy's future inventions. Pet. App. 13a-14a. The court held that Bayh-Dole was inapposite to the question to whom Holodniy had assigned his invention. *Id.* at 19a, 21a.

As discussed above, that analysis was flawed. The Federal Circuit should have first analyzed what right Holodniy had to the invention under Bayh-Dole. Holodniy's right under Bayh-Dole to own the invention was doubly contingent, and depended both on Stanford declining to exercise its right to retain title and on NIH, as the federal funding agency, approving an application by Holodniy to leave title with him, subject to the reservation of federal rights. 35 U.S.C. 202(d). Because Stanford *did* elect to retain title to the invention and because NIH *did not* approve an application by Holodniy to retain title himself, Holodniy had no rights that he could convey to Cetus through the VCA. See *Hydranautics*, 982 F.2d at 1553 (under pre-Bayh-Dole statute, purported assignee of inventor employed by federal contractor lacked standing to sue on the patent because the inventor "had no right to assign it"); *Heinemann*, 796 F.2d at 456 (under E.O. 10096, in-

vention of federal employee was "not the property of" the inventor, but rather was "the property of the Government," despite absence of valid assignment).

By making a university's ownership of federally funded inventions turn on the language of prior assignments by the inventor, of which the university might have no actual knowledge, the court of appeals' decision makes it virtually impossible for a university and a prospective industry licensee to be certain that the university owns the invention in question. They must prove a negative—that no co-inventor ever prospectively assigned his or her rights to a third party. To prevent the loss of patent rights (or identify that the rights are lost and truncate the investment in that technology), a university's or industry collaborator's lawyers must comb through every possibly relevant document, including seeking documents from any third parties with which the university's researchers might have interacted. Such virtually unbounded searches would constitute a far worse waste of patent lawyer resources than existed under the regime that Bayh-Dole was intended to correct. *See* Senate Report 30 (condemning the "onerous burden" of "trying to determine the ownership of patents arising from the agencies' research and development grants and contracts"). Moreover, the Federal Circuit's decision actually creates an incentive for companies to utilize VCAs or similar devices to entice university researchers to make private, secret assignments that might reduce (or eliminate) future royalty payments to the university or, alternatively, cloud the title of patents licensed to their competitors. No matter how much effort is expended, it will be impossible for a university and its licensee ever to

know with certainty that no such third-party assignment exists.

Given the large sums of money that must frequently be invested to develop a basic scientific invention into a marketable product, the uncertainties created by the court of appeals' decision will substantially impede commercialization. Bringing a new drug to market, for example, can cost hundreds of millions of dollars in testing and clinical trials that can last a decade. GAO Report 6-7, 10. A university and its licensee-collaborator, believing that title rested in the university, could therefore invest in a technology for over a decade only to face a title challenge at the time of commercialization. See *ibid.* The additional risk that the newly developed drug, even if safe and effective, would belong to some third-party assignee of the university researcher would inevitably lead some companies to forgo licensing universities' Bayh-Dole inventions, especially when those inventions are only at the very preliminary stages of product development.

While it is impossible to predict the precise number of commercialization arrangements that will not materialize, there can be no question that Bayh-Dole's objective of encouraging development of federally funded inventions will be undermined by the introduction of this additional uncertainty in licensing university patents.

2. Universities cannot protect themselves from the court of appeals' decision by changing their researcher contracts

In its petition-stage briefs, Roche argued that Stanford and other universities could "easily avoid the ruling below" by amending their researcher agreements "to grant immediate assignments" of interest in future inventions. Br. in Opp. 15. That argument is flawed as a matter of policy and inaccurate as a matter of fact.

a. To begin, Roche's argument that universities should respond to the Federal Circuit's decision by adopting "hereby assigns" language demonstrates that Roche's position in this litigation is not one of principle, but of opportunism. In the next case with facts like this one, if Roche's advice is followed, the industry collaborator will *not* obtain any ownership interest because the faculty researcher will already have assigned all his rights in future inventions to the university. Roche's argument, in other words, is "good for one ride only," with Roche the only rider.

b. Relegating ownership of Bayh-Dole inventions to the realm of competing assignment provisions cannot, in any event, provide the kind of certainty of title that is essential to the continued commercialization success of federally funded inventions. While inserting a "hereby assigns" provision in employment agreements might prevent a researcher from thereafter assigning away the university's Bayh-Dole rights, such a provision would be impotent to protect the university against "hereby assigns" contracts that the researcher already signed with a previous employer, when pre-

viously visiting a lab, or when engaging in earlier consulting arrangements.

Moreover, it is impossible to know that "hereby assigns" language will always be upheld as having priority over other formulations that have not yet been considered. Indeed, because issues of patent ownership can arise in the regional circuits, it is not even clear that other cases involving the same competing clauses will be resolved in the same fashion as this case.

c. Finally, changing contractual terms prospectively cannot eliminate the problems created by the Federal Circuit's decision regarding inventions that have already been conceived, or research already performed, under employment contracts that utilize the "agree to assign" language. Many inventions made under such agreements are only now entering the lengthy product development phase, and many more inventions will be conceived over the next decade for which ownership disputes will arise based on patent assignments and confidentiality agreements signed long ago. See GAO Report 6-7, 10. The Federal Circuit's decision casts a shadow on the effective commercialization of inventions deriving from billions of dollars in past, current, and ongoing federal research funding.

Congress enacted Bayh-Dole with the specific purpose of providing universities and other nonprofits with certainty that they would own their federally funded inventions and could enter into collaborative licensing arrangements to commercialize them. Bayh-Dole has been incredibly successful in achieving those goals, but the uncertainties generated by the Federal Circuit's decision now threaten that success. Making ownership of Bayh-Dole inventions turn on dueling assignment

provisions benefits no one other than Roche in this particular case. That is no justification for undermining one of the greatest legislative achievements in the past half century.

CONCLUSION

The judgment of the court of appeals should be vacated.

Respectfully submitted,

DOUGLAS HALLWARD-DRIEMEIER
JAMES R. MYERS
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DECEMBER 2010

APPENDIX

APPENDIX A

EX. ORD. NO. 10096. UNIFORM GOVERNMENT PATENT POLICY FOR INVENTIONS BY GOVERNMENT EMPLOYEES

Ex. Ord. No. 10096, Jan. 23, 1950, 15 F.R. 389, as amended by Ex. Ord. No. 10695, Jan. 16, 1957, 22 F.R. 365; Ex. Ord. No. 10930, Mar. 24, 1961, 26 F.R. 2583, provided:

NOW, THEREFORE, by virtue of the authority vested in me by the Constitution and statutes, and as President of the United States and Commander in Chief of the armed forces of the United States, in the interest of the establishment and operation of a uniform patent policy for the Government with respect to inventions made by Government employees, it is hereby ordered as follows:

1. The following basic policy is established for all Government agencies with respect to inventions hereafter made by any Government employee:

(a) The Government shall obtain the entire right, title, and interest in and to all inventions made by any Government employee (1) during working hours, or (2) with a contribution by the Government of facilities, equipment, materials, funds, or information, or of time or services of other Government employees on official duty, or (3) which bear a direct relation to or are made in consequence of the official duties of the inventor.

(b) In any case where the contribution of the Government, as measured by any one or more of the criteria set forth in paragraph (a) last above, to the invention, is insufficient equitably to justify a requirement of

assignment to the Government of the entire right, title and interest to such invention, or in any case where the Government has insufficient interest in an invention to obtain entire right, title and interest therein (although the Government could obtain some under paragraph (a), above), the Government agency concerned, subject to the approval of the Chairman of the Government Patents Board (provided for in paragraph 3 of this order and hereinafter referred to as the Chairman), shall leave title to such invention in the employee, subject, however, to the reservation to the Government of a non-exclusive, irrevocable, royalty-free license in the invention with power to grant licenses for all governmental purposes, such reservation, in the terms thereof, to appear, where practicable, in any patent, domestic or foreign, which may issue on such invention.

(c) In applying the provisions of paragraphs (a) and (b), above, to the facts and circumstances relating to the making of any particular invention, it shall be presumed that an invention made by an employee who is employed or assigned (i) to invent or improve or perfect any art, machine, manufacture, or composition of matter, (ii) to conduct or perform research, development work, or both, (iii) to supervise, direct, coordinate, or review Government financed or conducted research, development work, or both, or (iv) to act in a liaison capacity among governmental or nongovernmental agencies or individuals engaged in such work, or made by an employee included within any other category of employees specified by regulations issued pursuant to section 4(b) hereof, falls within the provisions of paragraph (a), above, and it shall be presumed that any invention made by any other employee falls within the provisions of paragraph (b), above. Either presumption may be

rebutted by the facts or circumstances attendant upon the conditions under which any particular invention is made and, notwithstanding the foregoing, shall not preclude a determination that the invention falls within the provisions of paragraph (d) next below.

(d) In any case wherein the Government nether (1) pursuant to the provisions of paragraph (a) above, obtains entire right, title and interest in and to an invention nor (2) pursuant to the provisions of paragraph (b) above, reserves a non-exclusive, irrevocable, royalty-free license in the invention with power to grant licenses for all governmental purposes, the Government shall leave the entire right, title and interest in and to the invention in the Government employee, subject to law.

(e) Actions taken, and rights acquired, under the foregoing provisions of this section, shall be reported to the Chairman in accordance with procedures established by him.

2. Subject to considerations of national security, or public health, safety, or welfare, the following basic policy is established for the collection, and dissemination to the public, of information concerning inventions resulting from Government research and development activities:

(a) When an invention is made under circumstances defined in paragraph 1(a) of this order giving the United States the right to title thereto, the Government agency concerned shall either prepare and file an application for patent therefor in the United States Patent Office [now Patent and Trademark Office] or make a full disclosure of the invention promptly to the Chairman, who may, if he determines the Government

interest so requires, cause application for patent to be filed or cause the invention to be fully disclosed by publication thereof: *Provided, however*, That, consistent with present practice of the Department of Agriculture, no application for patent shall, without the approval of the Secretary of Agriculture, by filed in respect of any variety of plant invented by any employee of that Department.

(b) [Revoked. Ex. Ord. No. 10695, Jan. 16, 1957, 22 F.R. 365]

3. (a) [Revoked. Ex. Ord. No. 10930, Mar. 24, 1961, 26 F.R. 2583]

(b) The Government Patents Board shall advise and confer with the Chairman concerning the operation of those aspects of the Government's patent policy which are affected by the provisions of this order or of Executive Order No. 9865, and suggest modifications or improvements where necessary.

(c) [Revoked. Ex. Ord. No. 10930, Mar. 24, 1961, 26 F.R. 2583]

(d) The Chairman shall establish such committees and other working groups as may be required to advise or assist him in the performance of any of his functions.

(e) The Chairman of the Government Patents Board and the Chairman of the Interdepartmental Committee on Scientific Research and Development (provided for by Executive Order No. 9912 of December 24, 1947), shall establish and maintain such mutual consultation as will effect the proper coordination of affairs of common concern.

4. With a view to obtaining uniform application of the policies set out in this order and uniform operations thereunder, the Chairman is authorized and directed:

(a) To consult and advise with Government agencies concerning the application and operation of the policies outlined herein;

(b) After consultation with the Government Patents Board, to formulate and submit to the President for approval such proposed rules and regulations as may be necessary or desirable to implement and effectuate the aforesaid policies, together with the recommendations of the Government Patents Board thereon;

(c) To submit annually a report to the President concerning the operation of such policies and from time to time such recommendations for modification thereof as may be deemed desirable;

(d) To determine with finality any controversies or disputes between any Government agency and its employees, to the extent submitted by any party to the dispute, concerning the ownership of inventions made by such employees or rights therein; and

(e) To perform such other or further functions or duties as may from time to time be prescribed by the President or by statute.

5. The functions and duties of the Secretary of Commerce and the Department of Commerce under the provisions of Executive Order No. 9865 of June 14, 1947 [set out above] are hereby transferred to the Chairman and the whole or any part of such functions and duties may be delegated by him to any Government agency or officer: *Provided*, That said Executive Order No. 9865 shall not be deemed to be amended or affected by any

provision of this Executive order other than this paragraph 5.

6. Each Government agency shall take all steps appropriate to effectuate this order, including the promulgation of necessary regulations which shall not be inconsistent with this order or with regulations issued pursuant to paragraph 4(b) hereof.

7. As used in this Executive order, the next stated terms, in singular and plural, are defined as follows for the purposes hereof:

(a) "Government agency" includes any executive department and any independent commission, board, office, agency, authority, or other establishment of the Executive Branch of the Government of the United States (including any such independent regulatory commission or board, any such wholly-owned corporation, and the Smithsonian Institution), but excludes the Atomic Energy Commission.

(b) "Government employee" includes any officer or employee, civilian or military, of any Government agency, except such part-time consultants or employees as may be excluded by regulations promulgated pursuant to paragraph 4(b) hereof.

(c) "Invention" includes any art, machine, manufacture, design, or composition or matter, or any new and useful improvement thereof, or any variety of plant, which is or may be patentable under the patent laws of the United States.

AMICUS CURIAE BRIEF

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IN THE

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Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., *et al.*,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF *AMICUS CURIAE* OF BIRCH BAYH IN SUPPORT OF PETITIONER

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Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF *AMICUS CURIAE* OF BIRCH BAYH IN SUPPORT OF PETITIONER

This Brief *Amicus Curiae* in support of Petitioner is filed by former United States Senator Birch Bayh.

INTEREST OF *AMICUS CURIAE* [1]

Amicus Curiae Birch Bayh served as United States Senator for the State of Indiana from 1963 to 1981.

[1] Pursuant to Supreme Court Rule 37.3, *Amicus Curiae* states that all parties have consented to the filing of this brief, and letters evidencing such consent have been filed with the Court. Pursuant to Supreme Court Rule 37.6, *Amicus Curiae* further states that no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *Amicus Curiae* or his counsel made a monetary contribution to its preparation or submission.

In that capacity, he was the co-principal Senate sponsor of the legislation ultimately enacted as the University and Small Business Patent Procedures Act, commonly known as the Bayh–Dole Act, 35 U.S.C. §§ 200–212 (2006). Senator Bayh has a long-standing commitment to scientific and technical innovation as a means of stimulating American economic growth. As a principal proponent of this statute, Senator Bayh retains an enduring interest in its proper construction and application.

Senator Bayh has previously submitted Briefs *Amicus Curiae* to this Court in 1981 and 2004.[2]

SUMMARY OF ARGUMENT

In 1980, Congress faced three vexing problems: (1) a national recession caused, in part, by a reduction in the country's competitiveness in international markets; (2) the insufficient commercialization of patents owned by the government and developed through federally-funded research by universities, small businesses, and nonprofit organizations; and (3) a hodge-podge of ineffective, inconsistent, and incoherent patent transfer policies. As a result of these problems, the creative genius of American inventors was not reaching the marketplace. Great American ideas were not leading to great American commercial successes.

Congress enacted legislation to address these problems. The Bayh–Dole Act determined that federally-funded patents should not and would not be warehoused in government bureaucracies. Rather, specified government contractors—universities, small

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[2] *See North Haven Bd. of Educ. v. Bell*, 456 U.S. 512, 526-527 (1982); *Jackson v. Birmingham Bd. of Educ.*, 544 U.S. 167 (2005).

businesses, and nonprofit organizations—were given the right and the responsibility to explore the development of these federally-funded innovations. The statute established clear and unequivocal rules on institutional ownership of patents for inventions developed by contractor organizations with federal research funding.

In the Bayh-Dole hierarchy, the ownership rights of contractors come first, followed by the government, with inventors last:

(1) Contractors "retain title" to all "subject inventions"—inventions "conceived or first actually reduced to practice in the performance of work done under a [federal] funding agreement." 35 U.S.C. §§ 201(e), 202(a).

(2) If a contractor fails to retain the invention, or chooses not to, the government can claim title, *see id.* § 202(c)(1)-(3), or "march-in" to develop the invention itself, *see id.* § 203.

(3) The inventor has no direct ownership interest in inventions developed with federal research funding, but only a provisional, subordinated ability to obtain title if the contractor and the government choose not to exercise their superior rights. Under the statute, neither the contractor nor the government requires an inventor's permission to develop their respective statutory rights. Rather, the nonprofit contractor has a responsibility to negotiate a share of royalties with an inventor. *See id.* § 202(c)(7)(B). In very limited circumstances, an inventor can request title if the contractor and government eschew their rights. *See id.* § 202(d).

Congress believed that this regime of explicitly-defined ownership rights would remove obstacles and enable American innovators to roar back into the market. This statutory scheme has now worked effectively for 30 years, resulting in thousands of commercialized inventions that might have otherwise lain fallow in government filing cabinets. Indeed, the Bayh–Dole Act has been called "[p]ossibly the most inspired piece of legislation to be enacted in America over the past half-century."[3]

The decision of the Federal Circuit improperly alters this regime by recognizing inventor rights (and inventor assignee rights) inconsistent with the Bayh–Dole Act hierarchy. The Bayh–Dole Act carefully balances the interests of all parties with interests in the discovery and commercialization of new technologies, but grants initial ownership rights to the research institution only, not the inventor it employed. The court below failed to recognize the provisional, subordinated nature of the innovator's interest, and its decision threatens to disrupt the careful balance of interests that Congress adopted.

The Court should answer the Question Presented by concluding that a federal contractor's ownership rights to inventions covered by the Bayh–Dole Act *cannot* be terminated unilaterally by an individual inventor through a separate agreement purporting to assign the inventor's rights to a third party.

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[3] *Innovation's Golden Goose*, The Economist Technology Quarterly, Dec. 12, 2002, at 3, *available at* http://www.economist.com/node/1476653?story_id=1476653.

ARGUMENT

I. CONGRESS ENACTED THE BAYH-DOLE ACT TO ADDRESS A FRAGMENTED FEDERAL TECHNOLOGY POLICY THAT COMPOUNDED AN AMERICAN PRODUCTIVITY SLUMP AND CAUSED THOUSANDS OF GOVERNMENT-FUNDED INVENTIONS TO GO UNUSED.

The Bayh-Dole Act was passed in 1980 to address a specific problem facing the United States. In the midst of a national recession, the federal government was spending huge sums of money to sponsor research and development at universities and small businesses, but very few of the patentable technologies resulting from this investment were reaching the marketplace. *See* S. Rep. No. 480, 96th Cong., 1st Sess., at 2 (1979) (*Senate Report*).

What made the recession so alarming was that, of its many causes, "an important factor [was] likely a slowdown in technological innovation in the United States" in the face of enhanced competition from overseas competitors in Europe and Asia.[4] *Id.* In the 1970s, for the first time since World War II, the United States' global leadership in productivity and innovation began to decline. The United States imported more foreign manufactured goods than ever before, resulting in a trade deficit in 1978 of $5.8 billion in those products. *Id.* at 1. At the same time, American businesses were spending less private

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[4] In 1980, the House Judiciary Committee warned that "the roots of the current recession lie in a longer term economic malaise which arises out of a failure of American industry to keep pace with the increased productivity of foreign competitors." H.R. Rep. No. 1307, 96th Cong., 2d Sess. Pt. 1, at 1 (1980).

money on research and development. *Id.* Moreover, small businesses—the traditional incubators of U.S. innovation and engines of job growth—were receiving a "distressingly low" percentage of federal research funding. *Id.*

Against this backdrop, as Congress began exploring new ways to stimulate the American technology sector, the troubled federal patent transfer system came to the fore of the debate.

A. Federal Agencies Employed a Host of Discordant Patent Transfer Policies.

Prior to the passage of the Bayh–Dole Act, federal agencies employed at least 24 different patent transfer policies, most of which were complex and occasionally contradictory. *See id.* at 2; H.R. Rep. No. 1307, 96th Cong., 2d Sess. Pt. 1, at 5 (1980) (*House Report*).

Most federal agencies required universities and small businesses to agree, as a precondition of federal funding, that ownership of all patentable inventions arising from federally-funded research would be retained by the sponsoring agency. *Senate Report* 2. In some instances, these agencies even required universities and small businesses to relinquish title to "background" inventions—*i.e.*, inventions created and owned independent of federal financial support—when those technologies were necessary to practice federally-funded inventions. Unfortunately, after obtaining title to the inventions they funded, these agencies would "follow the passive approach of making them available to private businesses," at no cost, for development and commercialization under non-exclusive licenses. *Id.*; *see* 126 Cong. Rec. 8742 (1980) (statement of Sen. Nelson).

Other agencies, such as the National Aeronautics and Space Administration, allowed grantees to retain title to federally-funded inventions only after they successfully completed lengthy waiver processes, in which the applicants were required to justify to the funding agency why they deserved to retain title. *See Senate Report* 2. These waiver processes were so cumbersome and time consuming that grantees often did not bother pursuing them to obtain ownership of their inventions.

A few innovative agencies, including the Department of Health, Education, and Welfare and the National Science Foundation, employed Institutional Patent Agreements ("IPAs"), which allowed prequalified universities and nonprofit organizations having technology transfer offices to retain title to inventions arising from federally-funded research. *See id.* at 21. The IPA programs proved extremely successful and led to the development and commercialization of numerous new drugs through the collaboration of universities and private industry. *See id.*

To replace these conflicting policies, the Bayh–Dole legislation was introduced to establish, by statutory mandate, a uniform patent transfer system across all federal agencies.

B. Federal Patent Ownership Policies Blocked Development of Government-Funded Inventions.

Although the federal patent policies preceding the Bayh–Dole Act led to the creation of thousands of patentable inventions, the vast majority of those inventions remained on government shelves, unlicensed, undeveloped, and unable to benefit the public. Of more than 28,000 patents owned by the

federal government, only four percent were licensed for development. *See id.* at 2. This depressing fact inspired the proponents of the Bayh–Dole Act to take action. *See id.* Existing patent policies had made federally-funded inventions freely available to all competitors—inconsistent with the core incentive of limited exclusivity afforded by the patent system. Congress concluded that this scheme, while well-intentioned, was misguided because none of the parties involved in the federal research and development process had sufficient incentives to commercialize new inventions.

In particular, universities, small businesses, and nonprofit organizations were unwilling to risk the effort and resources necessary to develop and commercialize federally-funded inventions. *See id.* The cost of marketing new products was at least 10 times the cost of the basic research that led to their conception. *See id.* at 19. Potential investors faced the risk that new technologies might ultimately prove unsuccessful in the marketplace or might not survive the regulatory approval process. *See id.* The adverse consequences of government ownership added further burdens to the considerable marketplace risks faced by innovators. *See id.*

Congress also concluded that the existing system ignored the economic reality that the funding agencies were poorly positioned to develop and commercialize new inventions arising from federally-supported research. The tasks of reviewing new inventions for commercial potential, advertising their availability, promoting their utilization, and negotiating their license were all formidable and beyond the experience of federal workers. *See, e.g., id.* at 30.

Congress also found that individual inventors had little incentive to remain involved with their discoveries given that, in most cases, title was completely claimed by the funding agency. This policy stifled commercialization. Separating inventors from their inventions was often catastrophic to the development of fledgling technologies. *See id.* at 22. The Senate Judiciary Committee noted that "[v]irtually all experts in the innovation process stress very strongly that such involvement by the inventor is absolutely essential, especially when the invention was made under basic research where it is invariably in the embryonic stage of development." *Id.*

As a result of these policies, nearly all of the patents developed by universities and small businesses with federal funding were "sitting unused under Government control," sometimes needlessly condemning people to suffer "because of the refusal of agencies to allow universities and small businesses sufficient rights to bring new drugs and medical instrumentation to the marketplace." *Id.* at 2; 126 Cong. Rec. 1796 (1980) (statement of Sen. Bayh). Mindful of its authority under the Spending Clause[6]

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[6] Under the Spending Clause of the Constitution, art. I, § 8, cl. 1, Congress has "wide latitude" to appropriate public funds, and to place conditions on the appropriation of public funds, in furtherance of the general welfare. *United States v. Am. Library Ass'n*, 539 U.S. 194, 203 (2003); *Nat'l Endowment for the Arts v. Finley*, 524 U.S. 569, 588 (1998). Courts defer to Congress' discretion when determining whether a particular expenditure, or a condition placed thereon, serves the general welfare. *See Mathews v. Castro*, 429 U.S. 181, 185 (1976) ("The discretion belongs to Congress, unless the choice is clearly wrong, a display of arbitrary power, not an exercise of judgment").

and the Patent and Copyright Clause[6] of the United States Constitution, Congress took action to facilitate the commercialization of technologies developed with federal research funding.

II. CONGRESS ENACTED THE BAYH–DOLE ACT TO STIMULATE COMMERCIALIZATION OF NEW TECHNOLOGIES BY PATENT OWNERSHIP REFORM.

The authors of the Bayh–Dole Act intended to design a new federal patent transfer policy that would tap the unrealized potential of federally-funded inventions. This goal would be achieved by assigning title to the entities best situated to ensure the commercialization of new technologies—namely, the universities, small businesses, and nonprofit organizations that participated in their discovery. The statute also replaced the numerous federal patent transfer policies with one uniform system that balanced the interests of all entities that participated in the development and commercialization process.

While the drafters anticipated the Bayh–Dole Act to be, at the least, "an important first step in turning around [America's] undesirable productivity and innovation slumps," *Senate Report* 29, in practice it became the "economic shot in the arm" that America

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[6] Under the Patent and Copyright Clause of the Constitution, art. I, § 8, cl. 8, "[t]he powers of Congress to legislate upon the subject of patents is plenary by the terms of the Constitution." *McClurg v. Kingsland*, 42 U.S. 202, 206 (1843); *see also Florida Prepaid Postsecondary Educ. Expense Bd. v. College Sav. Bank*, 527 U.S. 627, 648 (1999) (Stevens, J. dissenting). Courts "defer substantially to Congress" when determining whether a law is a rational exercise of legislative power under the Patent and Copyright Clause. *Eldred v. Ashcroft*, 537 U.S. 186, 204–05 (2003) (copyright case).

sorely needed to help restore its technological vitality. 126 Cong. Rec. 1798 (1980) (statement of Sen. Thurmond).

A. Congress Empowered Universities, Small Businesses, and Nonprofit Organizations to Commercialize Federally-Funded Technologies by Providing Them a Priority Right to Patent Ownership.

The Bayh-Dole Act, by operation of law, presumptively and automatically vests ownership rights in inventions arising from federally-funded research in the universities, small businesses, and nonprofit organizations responsible for their creation. *See House Report* 5. Congress did not provide for individual inventors to have transferable ownership interests in patentable inventions created with federal funding. Rather, Congress rewarded individual inventors by requiring their employers to provide them with a share of royalties to be negotiated with the universities or nonprofit organizations. *See* 35 U.S.C. 202(c)(7)(B); *Senate Report* 22. Congress concluded that this allocation of rights would promote commercialization, while providing an adequate incentive for inventors to remain involved in the early-stage development of their inventions. *See Senate Report* 22.

Congress elected to give universities, small businesses, and nonprofit organizations "preferential treatment" in the new federal patent transfer system in order to provide a more "attractive business opportunity" to private sector developers that were "unwilling to take a non-exclusive license under a Government-owned patent." *House Report* 5; *Senate Report* 18. Congress decided that these preferred

entities were in the best position to ensure "that inventions and processes arising from [federally-funded research would] be delivered to the marketplace as efficiently as possible." *Senate Report* 29.

Congress chose to give universities and nonprofit organizations the lead role because they received a large portion of federal research funding and "are much more efficient in delivering these important discoveries to the marketplace than are the agencies." *Id.* at 29. For example, in 1977, the federal government provided $3.35 billion in research support to universities, hospitals, and other nonprofit organizations. *See id.* at 19. As a result, these institutions conducted 68 percent of the country's basic research—"by far the biggest percentage" in the United States. *Patent Policy: Joint Hearing Before the S. Comm. on Commerce, Sci., and Transp. and the S. Comm. on the Judiciary*, 96th Cong., 2d Sess. 459 (1980) (statement of Sen. Bayh). Because so many patentable inventions arose from the basic research conducted by universities and nonprofit organizations, Congress concluded that these institutions—not federal agencies and not inventors—were best situated to manage and commercialize the resulting discoveries in collaboration with private industry.

Congress selected small businesses for their "impressive record as one of the leading sources of technological breakthroughs since World War II," and for their demonstrated "willingness to take risks that many larger companies [were] not willing to take in the pursuit of new technologies and products." *Senate Report* 29. Moreover, the drafters believed that small businesses would receive the greatest benefit from retaining title to patents invented by their employees because "a small business has fewer private resources

to develop and market raw products than their big business competitors." 126 Cong. Rec. 2004 (1980) (statement of Sen. Bayh).

B. Congress Adopted a Uniform and Balanced Patent Ownership Policy to Induce More Efficient and Predictable Technology Transfer.

In adopting the Bayh–Dole Act, Congress replaced the existing assortment of "at least 24 different patent policies in effect in the Federal agencies" with a single, uniform national policy for vesting patent rights in government-funded research. *Senate Report* 2.

Congress found that the federal patent policies in existence prior to the Bayh–Dole Act served as "artificial barrier[s], discouraging the commercialization" of federally-funded inventions. *Id.* at 29. They frequently presented costly roadblocks to universities and small business that lacked the legal expertise to navigate the labyrinthine maze of regulation standing between their inventions and the market. *See id.* at 3. Even agencies that permitted grantee institutions to retain patent rights to their inventions did so only after a lengthy decision-making process that served "to seriously jeopardize the ability of new inventions to be commercialized." *Id.* at 21.

In 1978, Senators Bayh and Dole compiled a list of 30 medical discoveries that had been delayed from nine months to more than a year while the funding agency determined whether to retain patent rights for itself. *See id.* at 21; 126 Cong. Rec. 8740 (1980) (statement of Sen. Bayh). To correct this problem, the legislation installed a streamlined patent transfer system to prevent "these promising inventions from

being suffocated under reams of unnecessary bureaucratic red tape." *Senate Report* 21. The statute was intended to ensure that new discoveries would be "commercialized as quickly as possible without the artificial restraints caused by the unnecessary delays and uncertainties . . . which only serve to make an already risky attempt to develop new products more of a burden on interested companies." *Id.* at 19.

By enacting the Bayh–Dole Act, Congress reduced the costs and risks of commercializing new ideas by making it easier for universities and small businesses to determine the nature and scope of their intellectual property rights. In particular, the statute presumptively permitted contractors to "elect to retain title" to federally-funded inventions rather than requiring them to petition the government for a waiver. 35 U.S.C. § 202(a). The statute also eliminated the risk to contractors that the government would force them to license their preexisting "background" inventions. *See id.* § 202(f). Along with predictability came reliability: universities and small businesses could rely on the statutory guarantee of clear title to their inventions, which, in turn, allows them to attract potential licensees and negotiate exclusive licenses, thereby hastening the commercialization of new technologies.

III. THE BAYH–DOLE ACT ESTABLISHES A CAREFUL BALANCE OF INTERESTS AMONG THE PUBLIC, THE GOVERNMENT, THE CONTRACTOR, THE PRIVATE DEVELOPER, AND THE INVENTOR.

The Bayh–Dole Act allocates ownership rights in patents for federally-funded inventions in a deliberate, hierarchical fashion, designed to balance the interests of each party participating in the patent

transfer process. Under the statute, universities, small businesses, and nonprofit organizations receive presumptive priority of title. The lowest rung of the hierarchy is reserved for individual inventors, who were intended to have only a provisional, and subordinated, opportunity to own technologies developed with federal funds.

The success of the Bayh-Dole Act is attributable to its deliberate and balanced distribution of rights and benefits among the stakeholders in federally-funded research and commercial development. The Federal Circuit's decision, allowing inventors to assign title to federally-funded inventions outside of the Bayh-Dole Act's carefully drawn parameters, would disturb this careful balance and undermine the statute's effectiveness.

A. The Statute Gives Universities, Small Businesses, and Nonprofit Organizations Presumptive Ownership Rights to Patents, and an Inventor May Obtain an Ownership Interest Only if the Contractor Surrenders its Rights and the Funding Agency Approves.

The Bayh-Dole Act created a structural hierarchy for the American technology transfer system that has operated successfully for 30 years. In adopting the statute, Congress never intended that ownership of federally-funded inventions would be contingent in the first instance upon assignment agreements between inventors and their employers. Rather, Congress allocated priority of title, in descending order, first to grantee research institutions, second to fund-

ing agencies, and lastly to individual inventors.[7] The Federal Circuit decision below stands the statutory system on its head by giving the inventor first priority to ownership.

Congress intended for universities, small businesses, and nonprofit organizations to have the preeminent and presumptive right to "elect to retain title" to federally-funded inventions. *Id.* § 202(a).[8] Although the statute grants these contractors the primary opportunity to retain title, it also allows them to forego ownership by waiving title or by failing to comply with the statutory requirements for retaining title. In those instances, the statute expressly provides that ownership reverts to the agency responsible for funding the research giving rise to the subject invention. *See id.* §§ 202(a), 202(c)(1)-(3). Thus, the contractor and the funding agency, respectively, occupy the top two rungs of the Bayh–Dole Act's three-tier hierarchy.

In contrast, the individual inventor does not receive any ownership interest in inventions discovered by federally-funded research. Congress instead gave the inventor an opportunity to receive reasonable compensation for any successful commercialization resulting from his inventions through negotiation

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[7] Congress did not include large private corporations that develop and commercialize federally-funded inventions in this hierarchy. Instead, these entities were expected to take exclusive licenses from the contractor institution under the statute. *See generally* 35 U.S.C. § 202.

[8] The House Judiciary Committee explicitly stated that Congress intended to "establish[] a *presumption* that ownership of all patent rights in government-funded research will vest in any contractor who is a nonprofit research institution or a small business." *House Report* 5 (emphasis added).

with the university or nonprofit organization. *See id.* § 202(c)(7)(B) (instituting "a requirement that the contractor share royalties with the inventor").

Only in exceptional and clearly defined circumstances may the inventor receive title under the statute. First, the contractor must decline title. *See id.* § 202(a). Second, the funding agency must take title. Third, the individual inventor must then petition the funding agency for title. *See id.* § 202(d). Indeed, the inventor may not even petition the funding agency for title unless and until the contracting entity declines title and the funding agency takes ownership. *See id.* § 202(d). If the inventor files such a petition, the funding agency must consult with the university, small business, or nonprofit organization before issuing an explicit decision granting or denying the inventor's request for ownership. *See id.* § 202(d).

Thus, Congress subordinated the inventor's ability to obtain title to the invention in the interest of greater development and commercial use of patents developed with federal funding. This deliberate decision is shown by the explicit language of the Act, requiring both an explicit surrender of title by the contractor and the agency's express approval before the individual inventor can take title to a federally-funded invention. *See* 35 U.S.C. § 202(d).

B. The Bayh–Dole Act's Success Lies in Its Precise Balance of the Rights and Interests of the Entities That Participate in the Patent Transfer Process.

For three decades, the public has benefitted from the positive effects of the Bayh–Dole Act. The Association of University Technology Managers recently

reported that more than 6,000 new domestic companies have arisen from university inventions, and nearly 5,000 new products have come onto the market, as a result of university patent licensing of federally-funded inventions in every significant field of technology.[9] A separate study has shown that 153 new pharmaceuticals resulting from federally-funded research have been brought to market since the law was passed.[10] The biotechnology industry has calculated that the Bayh-Dole Act has increased the United States gross domestic product by $187 billion, producing 279,000 new jobs between 1996 and 2007 alone.[11]

An essential feature of the Bayh–Dole Act is its precise balancing of the divergent interests of all the parties involved in the discovery and commercialization of new technologies. The statute has gone largely unchallenged in the courts until now, due to Congress' success in accommodating the divergent

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[9] *See* Association of University Technology Managers, Inc., *AUTM U.S. Licensing Activity Survey, FY2006: A Survey Summary of Technology Licensing (and Related) Performance for U.S. Academic and Nonprofit Institutions, and Patent Management and Investment Firms* (2006), *available at http://www.autm.net/AM/Template.cfm?Section=Home&CONTENTID=3954&TEMPLATE=/CM/ContentDisplay.cfm*

[10] *See* Ashley J. Stevens *et al.*, *The Contribution of Public Sector Research to the Discovery of New Drugs and Vaccines* presented at PraxisUnico Annual Meeting, Nottingham, United Kingdom (June 16, 2010), *available at* http://www.praxisunico.org.uk/uploads/Ashley%20Stevens.pdf.

[11] David Roessner, Jennifer Bond, Sumiye Okubo, & Mark Planting, *The Economic Impact of Licensed Commercialized Inventions Originating in University Research, 1996-2007*, 7-8 (Sept. 3, 2009), *available at* http://www.bio.org/ip/techtransfer/BIO_final_report_9_3_09_rev_2.pdf.

interests of its beneficiaries—namely, the public, the government, the contractor, the private sector developer, and the inventor.

1. The Bayh–Dole Act benefits the general public, in their capacities as both consumers and taxpayers, by ensuring that tax dollars invested in federal research and development return social and economic dividends.

The public benefits because new products and technologies have been brought to market, instead of having the underlying inventions sit undeveloped on government shelves. The drafters of the statute knew that an idea that is "frustrated and never gets out on the marketplace is, for all intents and purposes, worthless so far as helping the American people are concerned." 126 Cong. Rec. 1797 (1980) (statement of Sen. Bayh). In addition, because the law requires universities and nonprofit organizations to use the net proceeds of their licensing efforts to fund further "scientific research and education," the public continues to benefit from the further advancement of science and the self-reinforcing creation of additional technologies. 35 U.S.C. § 202(c)(7)(C).

The public also enjoys the economic stimulus and enhanced tax revenues that result when new technologies enter domestic and global markets. Moreover, the Bayh–Dole Act creates jobs by requiring that universities, small businesses, or nonprofit organizations that grant "exclusive right[s] to use or sell any subject invention" ensure that their licensees will manufacture the licensed products "substantially in the United States." *Id.* § 204.

2. The Bayh–Dole Act reserves key rights to the federal government as sponsor of this scientific

research, thus further protecting the public interest. When a contractor elects to retain title, the funding agency is entitled to a "nonexclusive, nontransferable, irrevocable, paid-up" license in the federally-funded invention. *Id.* § 202(c)(4). The funding agency also is empowered to monitor the commercialization efforts of the contractors by obtaining occasional reports on the development of federally-funded inventions. *See id.* § 202(c)(5). Furthermore, the Bayh–Dole Act permits federal agencies to "march-in" and license federally-funded inventions, even if the contractor has retained title, when the agency determines that the entity has not taken reasonable steps toward achieving practical application of the invention. *See id.* § 203. Finally, the Act allows the funding agency to take title to inventions arising from federally-supported research that implicate sensitive government interests, or when the government intends to develop the research to the point of utilization. *See id.* § 202(a).

3. Universities, small businesses, and nonprofit organizations are entrusted, as stewards of the public interest, to commercialize new technologies arising from federally-funded research. The Bayh–Dole Act gives these contractors a priority right to "elect to retain title" to inventions arising from federal grants, subject to mandatory procedural requirements. *See id.* § 202(a). Moreover, the Act permits these entities to obtain royalties by granting exclusive licenses to private corporate developers interested in commercializing new technologies. *See id.* § 202(c)(7). The statute also protects their "background" inventions by strictly limiting the government's ability to force contractors to license these inventions to only the rarest of circumstances. *See id.* § 202(f).

4. Private sector entities that seek to develop and commercialize new technologies also benefit from the predictability afforded by the Bayh-Dole Act. Rather than permitting such businesses to obtain title to patent rights in federally-funded inventions, the Bayh–Dole Act provides several other paths by which they may reliably acquire exclusive rights to develop and market promising new technologies. First, the Act enables universities, small businesses, and nonprofit organizations to grant exclusive licenses to private sector entities interested in incurring the risk and expense of developing federally-funded inventions for commercial sale. *See id.* § 202(c)(7). This allows the parties to conduct license negotiations with the assurance that the contracting party possesses clear title and can convey it. This reduces substantially the expense of due diligence as to title and the risk of patent litigation.

Second, if the contractor fails to retain or maintain title to a federally-funded invention, the Bayh–Dole Act allows the government to "march-in" and grant private sector entities exclusive licenses. *See id.* § 203. This ensures that a contractor will not unreasonably deny private developers the right to commercialize federally-funded inventions. Finally, the statute allows private sector developers to engage in negotiations with universities, small businesses, and nonprofit organizations, rather than legally unsophisticated inventors or cumbersome bureaucratic agencies.

5. The Bayh–Dole Act does not give individual inventors a direct right to any ownership interest in federally-funded inventions covered by the statute. Rather, Congress concluded that new advances would move more quickly from the laboratory to the medi-

cine cabinet if the Bayh–Dole Act recognized and rewarded the contributions of inventors in a different manner. To that end, the statute provides that universities and nonprofit organizations should enter into discussions with their inventors to determine a fair allocation of royalties arising from successful inventions. *See id.* § 202(c)(7)(B); *see also Senate Report* 22. By giving "special recognition" to inventors, Congress sought, successfully, to keep inventors involved with their discoveries through the commercial development process in order to bring new technologies to the market more rapidly. *Senate Report* 22, 33. In addition, by reducing the obstacles to successful commercialization of federally-funded inventions, Congress sought to expand the pool of royalties from which inventors would be compensated.

Thus, the Bayh–Dole Act struck a careful balance among the varying interests of the many stakeholders whose concerted efforts are needed to put new ideas to work in the marketplace. The balance established by the statute has provided an effective, predictable, and flexible set of incentives and restrictions that has greatly facilitated the negotiation of mutually beneficial technology transfer agreements, and the resulting transformation of federally-funded innovations into commercially successful products.

C. The Policies and Provisions of the Bayh–Dole Act Demonstrate Congress' Clear Intent That Universities, Small Businesses, and Nonprofit Organizations Should Hold Title to Federally-Funded Inventions, Not Individual Inventors.

The remarkable success of the Bayh–Dole Act would be compromised if inventors were allowed to

trump the interests of the public, the contractors, the federal government, and the private developers by independently assigning title to federally-funded inventions. The balance Congress struck in the statute would be fundamentally disrupted by an interpretation which concluded that inventors hold any ownership interest in patents obtained through federally-funded research, much less title that can be independently transferred away from the government-funded research organization.

The language of the Bayh–Dole Act clearly evidences the legislature's intention to vest patent rights in universities, small businesses, and nonprofit organizations, rather than individual inventors. The law's requirement that contractors share resulting royalties with their inventors constitutes solid evidence that the drafters intended that individual inventors themselves would not own title to patents developed with federal funds. *See* 35 U.S.C. § 202(c)(7)(B).

Congress determined that inventors would have only a provisional, subordinated ability to obtain ownership in limited circumstances. This is plain from multiple provisions of the Bayh-Dole Act, including: (1) universities, small businesses, and nonprofit organizations are entitled to "elect to retain title" to inventions, not the inventors, *see id.* § 202(a); (2) contractors, not their employee inventors, are responsible for disclosing new technologies to funding agencies, *see id.* § 202(c)(1); (3) contractors are prohibited from assigning title to *anyone* except patent management organizations, *see id.* § 202(c)(7)(A); and (4) if the contractor elects not to retain title to an invention, patent rights vest in the funding agency, not the inventor; the inventor must thereafter seek

and obtain explicit approval from the funding agency before he or she may obtain those rights, *see id.* § 202(d).

Finally, the Bayh–Dole Act establishes the fundamental basis of technology transfer relationships for research institutions by requiring contractors to negotiate exclusive licenses with private sector developers to commercialize federally-funded inventions. The Act supports this crucial relationship by establishing a system in which it is certain that the grantee research institution possesses, and can convey, clear title to the invention. Universities, small businesses, and nonprofit organizations cannot efficiently commercialize new technologies if they are unable to demonstrate such clear title.

By assuring that the contractors would have clear title, the Bayh Dole Act also benefits private sector developers to minimize the costs of due diligence concerning ownership interests, which would otherwise create substantial disincentives to commercializing new inventions.

In sum, the language and legislative history of the Bayh–Dole Act are unequivocal. Congress intended to vest title to federally-funded inventions in the hands of those best suited to ensure their efficient commercialization—the research institutions, not their employees. Congress never envisioned that individual inventors would have any rights to assign except those subordinated rights that they might obtain from the funding agency through a multi-step statutory framework. To allow inventors to assert title and transfer it freely would destroy the carefully crafted and finely balanced mechanism that Congress established and that has served the public interest greatly for the past three decades.

CONCLUSION

For the reasons set forth above, *Amicus Curiae* respectfully submits that the Court should conclude that a university, small business, or nonprofit organization's ownership of inventions arising under the Bayh–Dole Act *cannot* be terminated unilaterally by an individual inventor through a separate agreement purporting to assign the inventor's rights to a third party.

Respectfully submitted,

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In The
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BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., et al.,

Respondents.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF OF *AMICUS CURIAE* BAYHDOLE25, INC. IN SUPPORT OF PETITIONER

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INTEREST OF *AMICUS CURIAE*[1]

BayhDole25, Inc. ("BayhDole25") is a non-profit, non-governmental organization named for the Bayh-Dole Act of 1980 ("Bayh-Dole") and related legislation, and founded on the twenty-fifth anniversary of passage of the Act. BayhDole25 does not receive federal funding, nor has it received financial support from research institutions, universities, or individual biotechnology companies. BayhDole25's mission is to increase awareness of the importance of Bayh-Dole for creating and commercializing new technologies for economic and social benefit. Since incorporation in 2006, BayhDole25 and its Board have made important contributions to the understanding of public policy priorities relating to technology transfer and the key role of Bayh-Dole in continued United States global competitiveness, particularly in the area of the life sciences.[2]

BayhDole25's educational materials, capacity building programs and web site have become "go-to" resources for policy makers domestically and around

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[1] Pursuant to this Court's Rule 37.3(a), BayhDole25 understands that letters of blanket consent from all parties to the filing of this brief have been submitted to the Clerk. Pursuant to this Court's Rule 37.6, *amicus* states that this brief was not authored in whole or in part by counsel for any party, and that no person or entity other than *amicus* or its counsel made a monetary contribution to fund the preparation or submission of this brief.

[2] BayhDole25 publications and related presentations are available online at: http://www.bayhdole25.org/resources (last visited December 21, 2010).

the world.[3] Since 2006, BayhDole25 has participated in numerous science and technology programs in the United States, as well as in Brazil, China, Chile, France, India and Italy, where the benefits of a Bayh-Dole-type approach have been showcased as the way to commercialize public investment in scientific research. The technology transfer scheme of Bayh-Dole, in which ownership of government funded inventions are maintained by the research entities, has been emulated around the world with great success. *See* THE BAYH-DOLE ACT AT 25, at 37-44 (Apr. 17, 2006) (hereinafter "BAYHDOLE25 WHITEPAPER") (citing both Organization for Economic Co-operation and Development ("OECD") members and advanced developing countries that have benefited from adoption of technology transfer statutes or related mechanisms.)[4]

The Parties and other *amici curiae* represent the interests of federally funded contractors, research

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[3] For example, BayhDole25 publications already have been cited in this appeal by *amicus curiae* Massachusetts Institute of Technology in its Brief in Support of Petitioner for Writ of Certiorari, at 6, 8. Internationally, BayhDole25 publications have been cited by policy makers in South Africa and India. Closer to home, the Levin Institute of the State University of New York recommends the use of BayhDole25's IP Toolkit for an understanding of intellectual property globalization. *See* http://www.globalization101.org/issue_sub/technology/suggestReadings/ (last visited on December 21, 2010).

[4] Available online at: http://www.bayhdole25.org/whitepaper (last visited on December 21, 2010).

institutions and universities, private sector businesses and, of course, the Government. All of these are important stakeholders in the Bayh-Dole statutory framework, in which research institutions and universities receive critical research funds as contractors to the Government, private industry transforms the resulting science and technological advances into commercially successful products and services, and the Government furthers its objective of promoting the commercialization and public availability of inventions made as a result of federally funded research projects. Although BayhDole25 is not an economic stakeholder, it has the broader mission of advocating for the powerful social and economic benefits that have flowed from Bayh-Dole. As such, BayhDole25 is uniquely situated to provide an additional perspective that may be useful to the Court.

SUMMARY OF ARGUMENT

Before the Bayh-Dole Act was enacted in 1980, federally funded scientific research resulted in little commercial development. A fundamental problem was that the Government retained ownership of the intellectual property resulting from that research, and there was often no clear process for transferring invention rights to the university or private industry sectors. In particular, universities and other nonprofit research organizations – the chief recipients of federal research dollars – often would not end up owning the patents for the inventions created from

their work.[5] Because the universities did not own the patent rights, they were hamstrung in their efforts to collaborate with the private sector to commercialize any innovations resulting from federally funded research because private industry would not invest in the development of technology it ultimately could not protect. As a result, very little federally funded research was ever commercialized. This problem prompted Senator Birch Bayh's famous comment: "What sense does it make to spend billions of dollars each year on government sponsored research and then prevent the new developments from benefitting the American people because of dumb bureaucratic red tape." *A Special Status Report from Birch Bayh*, NEWS FROM BIRCH BAYH (Apr. 23, 1980).

By passing Bayh-Dole and related technology transfer legislation, Congress created a strong federal policy encouraging private development of publicly funded research. Bayh-Dole created the needed economic incentives for commercialization, largely through its clear ownership scheme in which "contractors" (universities, other non-profit research organizations and small businesses receiving federal research funding) can "elect to retain title to any subject invention" (*i.e.*, any invention of the contractor conceived or first reduced to practice in the performance

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[5] One study indicated that before 1980, fewer than 250 patents were issued to United States universities each year. *See* BAYHDOLE25 WHITEPAPER, at 23. In contrast, in 2003, 3,933 patents were issued to United States universities. *Id.*

of work under a funding agreement) by following the steps set out in the statute. 35 U.S.C. §§ 201, 202.

The economic results from this clarity have been dramatic. One survey of university licensing activity noted that between 1993 and 2003 alone, over 32,000 patents were issued from federally funded research, and over 4,000 companies were created as a result of federally funded university research between 1980 and 2003. *See* AUTM Licensing Survey: FY 2003 Survey Summary, at 3-4, 28 (Ashley J. Stevens & Frances Toneguzzo, eds., Assoc. of Univ. Tech. Mgrs., Northbrook, Illinois 2004). A similar recent survey reported that in 2009, 658 new commercial products were introduced, 5,328 licenses and options were executed, 596 new companies were formed, 3,423 startup companies were still operating, and there had been $53.9 billion in total sponsored research expenditures. *See* AUTM U.S. Licensing Activity Survey: FY 2009 (Survey Summary).[6]

As the National Institutes of Health ("NIH") has reported to Congress:

> It is impossible to overstate the achievements of the global macroeconomic impact

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[6] Available online at http://www.autm.net/AM/Template.cfm?Section=Licensing_Surveys_AUTM&TEMPLATE=/CM/ContentDisplay.cfm&CONTENTID=5239 (last visited December 21, 2010).

> of U.S. taxpayer-supported biomedical research. Federally funded biomedical research, aided by the economic incentives of Bayh-Dole, has created the scientific capital of knowledge that fuels medical and biotechnology development. American taxpayers, whose lives have been improved and extended, have been the beneficiaries of the remarkable medical advances that have come from this enterprise.

National Institutes of Health: *NIH Response to the Conference Report Request for a Plan to Ensure Taxpayers' Interests are Protected* (July 2001).[7]

BayhDole25 believes that the Federal Circuit's holding, if not reversed, threatens a return to the pre-Bayh-Dole "bad old days" when uncertainty about the ownership of inventions from federally funded projects thwarted university and industry collaboration — collaboration that, when allowed to flourish, has created remarkable medical and scientific advances leading to numerous new companies and jobs for our economy.

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[7] Available online at http://www.nih.gov/news/070101wyden.htm (last visited December 21, 2010).

ARGUMENT

I. THE FEDERAL CIRCUIT'S INTERPRETATION OF BAYH-DOLE WILL FRUSTRATE TRILATERAL GOVERNMENT / RESEARCH INSTITUTION / PRIVATE SECTOR COOPERATION TO THE DETRIMENT OF THE UNITED STATES ECONOMY

The Federal Circuit's opinion creates new, destructive uncertainties regarding title to federally funded inventions. These new uncertainties are different than those which existed in the pre-Bayh-Dole regime, but they will be every bit as frustrating and counterproductive to the commercialization of federally funded inventions. Before Bayh-Dole, the uncertainty lay in whether the Government, on the one hand, or the federally funded contractor, on the other hand, would ultimately obtain title to the invention. The answer to that question had been determined by a complex patchwork of regulations, which varied in terms and scope with each federal agency involved. *See* H.R. Rep. No. 96-1307, Pt. 1 at 3 (1980).

Bayh-Dole's simple yet robust framework replaced the regulatory patchwork, and calmed uncertainty over ownership of federally funded inventions. In the thirty years since Bayh-Dole's enactment, the United States has enjoyed the benefits of unprecedented scientific advancement from federally funded research, resulting in billions of dollars of economic activity, countless technology transfers, and the creation of an impressive array of innovative products

and services and millions of jobs. *See* BAYHDOLE25 WHITEPAPER, at 22-25. This scientific and economic prosperity was fostered in large part by the certainty of title created by Bayh-Dole, which carefully balances the potentially competing interests of the Government, research institutions, and the private sector. For its part, the Government has an interest in receiving a tangible return on taxpayer dollars invested in federally funded research projects. Nonprofit federal contractors – universities and other research institutions – have an interest in obtaining a stream of royalty payments from the inventions created from federally funded research, which they then can reinvest in additional research and education, and also use to fulfill the important mandate of promoting local or regional economic development.[8] *See, e.g.*, 35 U.S.C. § 202(c)(7). The private sector has an interest in developing and marketing commercially successful products from their collaboration with federal contractors, such as research institutions like Stanford.

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[8] "'The data reported by universities reveal that academic technology commercialization continued to thrive even in the midst of the global financial crisis, providing a steady stimulus to the economy' says Ashley J. Stevens, DPhil. (Oxon), CLP, AUTM president. 'The majority of the startups formed are located in the licensing institution's home state, which demonstrates that the Bayh-Dole Act continues to have a major impact on local economies across the nation,' adds Stevens." Gene Quinn, *AUTM Survey: University Licensing Strong Despite Economy* (Dec. 17, 2010) available online at: http://ipwatchdog.com/2010/12/17/autm-survey-university-licensing-strong-despite-economy/id=13845/ (last visited December 22, 2010).

The certainty of title created by Bayh-Dole has resulted in unparalleled trilateral cooperation between the Government, research institutions, and the private sector the likes of which had not been seen before. Put simply, Bayh-Dole's framework of clearly defined rights to title in federally funded inventions, coupled with clearly defined statutory responsibilities of each party, made cooperation between the Government, research institutions and the private sector possible. The resulting commercialization of scientific research has enabled unprecedented social and economic value through the creation of new lifesaving and life enhancing medical and other technologies.

In sharp contrast, the Federal Circuit's opinion has brought turmoil into this well-established and understood trilateral relationship. The opinion below has rolled back the clock and replaced the pre-Act uncertainty about title with a new, equally destructive one: namely, whether an inventor with the stroke of a pen can divest the Government, research institution, and private industry from the fruits of their multi-million dollar investments. Under the Federal Circuit's interpretation of Bayh-Dole, none of these three key stakeholders can be sure of title to any federally funded invention. The uncertain answer to this question now rests not with a patchwork of multiple federal regulations (as in the past), but with the whims of individual inventors who, according to the Federal Circuit opinion, have the unfettered right to assign their federally funded inventions without regard to Bayh-Dole's statutory provisions.

The immediate effect of the Federal Circuit's opinion will be to disrupt thirty years of cooperation

between the Government, research institutions, and the private sector. The ultimate effect, however, will be to diminish the advancement of practical scientific research in the United States, and roll it back to pre-Bayh-Dole levels. At a time when we face new economic challenges and uncertainties, as well as increasing competitive pressures from nations such as Brazil, Russia, India and China – the so-called BRICs – the United States can ill-afford to sabotage its own investment in technological advancement.[9]

If the Federal Circuit's opinion is affirmed, a private business collaborating with a federal contractor will not know whether the contractor will have full (or indeed any) rights to any resulting invention. For example, if, as the Federal Circuit holds, an individual inventor working under a federal funding agreement retains the right to assign her invention to anyone, the inventor would have the right to assign it to a non-collaborating third-party. Indeed, under the

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[9] "Brazil, Russia, India, and China will dominate future R&D growth, overwhelming Europe and Japan and, eventually, matching the investments in the U.S. At the current levels of spending, China alone will outspend Japan in R&D in mid-2010, match assumed aggressive spending in all of Europe combined in 2018, and match U.S. R&D spending in 2022." Martin Grueber and Tim Studt, *2010 Global R&D Funding Forecast: An Overview*, R&D MAGAZINE (Dec. 22, 2009), available online at http://www.rdmag.com/Featured-Articles/2009/12/Policy-and-Industry-2010-Global-R-D-Funding-Forecast-An-Overview/ (last visited December 22, 2010). *See also*, Gautam Naik, *China Surpasses Japan in R&D as Powers Shift*, Wall St. J., Dec. 15, 2010, at B4, available online at http://online.wsj.com/article/SB10001424052748703734204576019713917682354.html (last visited December 22, 2010).

rationale of the Federal Circuit's opinion, the inventor has *carte blanche* to unilaterally elect to retain the invention for herself, or to assign the rights to a third party for her own benefit without the knowledge or consent of the federal contractor. This holding is directly contrary to Bayh-Dole's statutory plan.

Without certainty of title to federally funded inventions, prudent private businesses will be reluctant to devote the time, human resources, and capital necessary to effectively collaborate with a non-profit research institution on a federally funded research project. Similarly, universities and other research institutions would be much less likely to encourage or permit their research scientists to meet with private industry experts for fear of losing future patent rights. This, in turn, will reduce the effective use of federal research dollars to promote truly innovative research.

The uncertainty created by the Federal Circuit's opinion also does violence to the Government's significant interest in ensuring that federally funded inventions are commercialized. Under Bayh-Dole, if the Government determines, for example, that the contractor or private sector licensee is not effectively commercializing the federally funded invention, the Government retains the right "to require the contractor, an assignee or exclusive licensee of a subject invention to grant" a license "to a responsible applicant or applicants" and, if the contractor, assignee, or exclusive licensee refuses, the Government may "grant such a license itself." *See* 35 U.S.C. § 203(a). But if an individual inventor retains the right to assign a federally funded invention to a third-party

(or to herself), the Government's rights to oversee and ensure the commercialization of the invention would be nullified, as would its "march-in" rights under Section 203(a) to reassign or reclaim title to the invention.

The Government therefore may be more reluctant in the future to give federal funding to any institution without first obtaining assurances from that institution that none of the researchers on the proposed research project have previously assigned any prospective rights in an invention to a third-party. Private industry will have the same concerns before investing in commercial activity arising out of Government funded research. The legal due diligence required to calm anxiety over ownership will take time and money, resulting in delays before commencement of any Government funding and any federal contractor / private sector collaboration. Even then, there would be no guarantee that a researcher would not subsequently assign "her" putative rights in any invention to a collaborating private business – as Roche contends occurred here – thereby frustrating the important interests of all Bayh-Dole participants in enjoying the fruits of federally funded research.

CONCLUSION

We now face a United States economy eerily similar to that which existed in the "malaise" of the 1970s that immediately preceded Bayh-Dole's passage. The economy is stagnant. Businesses are fearful due to uncertainties over future economic conditions

and government regulatory pronouncements. Consumer confidence is lackluster. Unemployment (among those seeking work) hovers around 10% with little relief in sight. Foreign competition looms large.

The United States simply cannot afford to stifle innovation, scientific advancement, and economic growth. Separate and apart from the Federal Circuit's legal error in ignoring the primacy of the Bayh-Dole Act's ownership framework, the Federal Circuit's decision will frustrate the settled economic expectations of the key stakeholders in the Bayh-Dole statutory scheme. The clear economic benefits that our economy has enjoyed from Bayh-Dole for the past thirty years are now jeopardized as a result of the Federal Circuit's incorrect interpretation of Bayh-Dole.

The Federal Circuit's opinion below was wrongly decided. It should be reversed.

Respectfully submitted,

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AMICUS CURIAE BRIEF

22

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BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY,
Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., *et al.*,
Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

BRIEF OF *AMICUS CURIAE* BIOTECHNOLOGY INDUSTRY ORGANIZATION IN SUPPORT OF RESPONDENT

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BRIEF OF BIOTECHNOLOGY INDUSTRY ORGANIZATION IN SUPPORT OF RESPONDENTS

The Biotechnology Industry Organization ("BIO") submits this brief as *amicus curiae* in support of respondents in this case.[1]

INTEREST OF *AMICUS CURIAE*

BIO is the country's largest biotechnology trade association, representing the biotechnology industry. It has over 1100 members, including academic institutions, startup businesses, large Fortune 500 corporations, and even university spin-offs and biotechnology centers. The biotechnology industry invests more than 20 billion dollars annually in research and development, and provides employment to hundreds of thousands of highly educated and highly skilled individuals. BIO members are involved in the process of discovering and bringing to market products in the healthcare, agricultural, environmental and industrial biotechnology fields.

The biotechnology industry exists today because of its close relationship to universities. In fact, many BIO members can trace their lineage to small startup companies formed by the partnership of a university researcher, who made a basic science discovery and saw its potential for a commercial application, with industry and other funding sources. These

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[1] Letters from Petitioner and Respondents indicating their consent to the filing of *amicus* briefs have been filed with the Clerk of this Court. Pursuant to Rule 37.6, *amicus curiae* states that no counsel for a party authored this brief in whole or in part, and no person or entity other than *amicus curiae* or its counsel made a monetary contribution to the preparation or submission of this brief.

partnerships between industry and academia are mutually beneficial to both institutions. They have proven not only essential to the delivery of tangible products and services to patients and the public generally, but also critical to the academic understanding of biotechnology as a coordinated set of scientific disciplines.

Patent rights are particularly important for biotechnology, where product development times are lengthy, and development costs are large. Developing a single biotechnology therapy requires an average investment of $1.2 billion, and the clinical testing period alone consumes more than 8 years on average. Joseph A. Di Masi & Henry G. Grabowski, *The Cost of Biopharmaceutical R & D: Is Biotech Different?*, 28 Managerial & Decision Econ. 469, 475 & tbl.3 (2007). Such investment is risky. For every successful biopharmaceutical product, thousands of candidates are designed, screened, and rejected after large investments have been made. Only a small minority even advance to human clinical trials, and most of those fail to obtain FDA approval. The chances that a biopharmaceutical medicine will advance from the laboratory bench to the hospital bedside are approximately one in 5,000. Tommy G. Thompson, Sec'y of Health & Human Servs., *Remarks at the Milken Institute's Global Conference* (Apr. 26, 2004), *available at* http://www.hhs.gov/news/speech/2004/040426.html.

The ability of biotechnology companies to obtain and control the transfer of ownership interests in patents has been a critical precondition to commercializing biotechnology inventions. BIO members work within a highly collaborative business environment, and rely on a web of relationships with different industry participants to shepherd the

development of a fundamental scientific discovery into tangible products and services. Moreover, based on the experience of BIO members, inventions do not come into being because of funding alone. Instead, inventions result from a serendipitous process, where inventors draw upon prior knowledge and intangible contributions of many partners working to a common end. Certainly, funding is essential to procure materials and services needed to carry out the research that results in inventions, but funding by itself is not the source of a conception or an actual reduction to practice of an invention.

The security of ownership interests in patents is of paramount concern to BIO's members. It is one of many necessary conditions that must be met before biotechnology businesses and their investors are willing to engage in such high-cost, high-risk product development and, thus, directly affects their ability to bring new products to the public. BIO members, accordingly, have a substantial interest in the law governing ownership of inventions made with federal funding and ensuring that the Bayh-Dole Act will continue to provide an effective incentive for the biotechnology industries to continue their extensive symbiotic relationship with universities.

BIO submits this brief to explain the potential negative and unforeseen consequences of Petitioner's proposed construction of the Bayh-Dole Act, which seeks to alter the well-accepted legal principle that the original ownership of an invention vests with the inventor.

SUMMARY OF THE ARGUMENT

The Bayh-Dole Act, since its enactment, has delivered innumerable benefits to the American public. These include not only new products and

services arising out of collaborative research that address unmet medical needs, or solve longstanding industrial and agricultural problems, but the advancements in basic scientific knowledge that result from the close collaborations encouraged by the Act between the private and public research communities. The Act also has greatly facilitated the rapid dissemination of basic research into commercially important technology, and with that, has helped fuel the growth of industries including obviously the biotechnology industry. By any measure, the Act has functioned precisely as its sponsors envisioned.

In the 30-plus years of experience under the Bayh-Dole Act, the legal status of the inventor as the original owner of an invention has never been called into question, much less presented an impediment to successful administration of the Act. Within this period, thousands of contracting agencies and private entities have routinely secured effective assignments of the rights of their inventors to inventions developed through their sponsorship These institutions likewise have administered those rights using straightforward contract law principles. Indeed, universities and biotechnology companies have been able to arrange myriad forms of research collaborations, all of which have effectively defined the interests of the parties in the inventions arising from these collaborations, while satisfying their obligations under the Bayh-Dole Act. In short, both private and public institutions have faced no challenges in using written contracts to transfer and manage the ownership of inventions that are subject to the Bayh-Dole Act in the same way they have used these contracts to manage ownership interests in non-federally-sponsored inventions. And, based on these

practices, the collaborative research and movement of federally-funded inventions from the laboratory to the market pursuant to that Act has flourished.

These longstanding practices are grounded on the principle that U.S. law defines the original owner of an invention to be the inventor. This principle has a Constitutional footing; in Article I, section 8, clause 8, the Constitution empowers the Congress to provide exclusive rights to "Inventors." And in every Patent Act passed by the Congress since then, this principle has remained undisturbed.[2] Construing the Bayh-Dole Act, which is part of the Patent Act, as having *sub silentio* changed this fundamental principle would completely distort the American concept of inventorship without a clear basis in the statute and while doing clear violence to the underlying purpose of the Bayh-Dole Act.

Certainly, a university or other federal grantee may, by contract, require an inventor to transfer her rights in an invention, and it may then further dispose of these acquired rights in accordance with the provisions of funding agreements required under the Act. Interpreting the Bayh-Dole Act to vest those rights originally in the contractor – effectively holding that an inventor never holds the initial rights in the invention he has made if the creation of that invention has been supported in any manner by federal funding – is neither necessary nor consistent with the Bayh-Dole Act or its purpose. For decades

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[2] Even in pending legislation, which now proposes to give the beneficial owner of an invention an enhanced right to file a patent application, Congress continues to leave this principle undisturbed. *See* The Patent Reform Act of 2011, S. 23, 112th Cong. § 3 (2011) (addressing revision to 35 U.S.C. §§ 115 (Inventor's Oath or Declaration) and 118 (Filing by other than inventor).

contractors, federal laboratories and private institutions have transferred ownership interests of the inventor through assignment contracts, successfully preserving the government's interests in inventions governed by the Bayh-Dole Act.

Indeed, the rule proposed by Petitioner would be inimical to the very nature of inventive conduct and technology development in the life sciences. Research collaborations that result in inventions are not predictable, simple or formulaic enterprises. Instead, as illustrated by this case, inventions frequently result from an inventor following a serendipitous path, where that inventor draws upon intangible contributions and know-how made available to gain critical insights that result in conception of the invention, and its reduction to tangible form. Scientists conceive of inventions quite independently of who funded their work, and the exchange of know-how, and use of insights provided through discussions with other scientists, usually plays a much more significant role in helping the inventor achieve the invention than financial support.

A rule that by operation of law awards original ownership of the invention to the contractor on the sole basis of federal funding will erect harmful barriers between scientists who perform work under federal funding agreements and others who do not. This is because such a rule will inherently undervalue any contributions made by non-federally-funded parties to achieve the invention. Such a rule would inhibit (rather than promote) the types of interactions between publically- and privately-funded researchers that the Bayh-Dole Act envisioned, because it will disproportionately empower contractors under the Act relative to third parties. A private party, required to operate under free market

economic principles, will choose to avoid both federal funding and interactions with institutions receiving that funding, because that private party will not have sufficient leverage to negotiate a shared ownership or control of the patented invention that reflects the value that party brings to the invention. And this fact alone will drive the private sector away from these types of arrangements.

Nothing in the Bayh-Dole Act can be read to suggest that Congress intended to empower universities in this way. Indeed, skewing the equation of shared interests in patented technology in this manner would fundamentally undermine the objectives of the Bayh-Dole Act, and will disrupt the collaborative environment that has served the public interest so well for the last 30 years.

Nor would the proposed rule contribute to the certainty of ownership of inventions that arose out of, or in collaboration with, federally-funded research institutions. To the contrary, it could

- call into question established agreements that have been entered into on the basis of the well-accepted legal principles governing original ownership of an invention;
- cloud ownership interests held by employers of private third party co-inventors where proper assignments have been executed;
- raise questions about the ownership of patents where the first actual reduction to practice was federally-sponsored after a patent on the conceived invention was granted to a private third party; and
- create uncertainties about the ownership of inventions where multiple federal grants, and

> multiple federal grantees were involved in the invention's conception or first actual reduction to practice.

There is no need to sever the fundamental link between inventorship and original ownership of an invention just to address isolated instances where federally-funded inventors might assign rights in violation of institutional policies. Equitable and contract remedies have long been available to give nonprofit research institutions the rights to which they are entitled and which they need to safeguard the funding agencies' interests.

Accordingly, BIO urges the Court to affirm that the Bayh-Dole Act did not alter the principle that the ownership of an invention originates in the inventor, and that obligations defined in the Act regarding ownership of inventions that have been supported by government money attach after this event has occurred.

ARGUMENT

I. THE BAYH-DOLE ACT BUILT UPON AND DID NOT CHANGE ACCEPTED PRINCIPLES OF INITIAL OWNERSHIP OF INVENTIONS

1. The sponsors of the Bayh-Dole legislation, aware of the scant number of federally-funded inventions that had been commercialized under existing funding policies, understood that federal grant recipients needed to be able to take control of their inventions without interference from the government bureaucracy. Rebecca S. Eisenberg, *Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research*, 82 Va. L. Rev. 1663, 1664 (1996) (the sponsors recognized

that "[i]f the results of federally-sponsored research were to be rescued from oblivion and successfully developed into commercial products, they would have to be patented and offered up for private appropriation.") The Bayh-Dole Act that passed had that basic goal in mind. It removed the red tape associated with the process of effecting transfers of previously existing interests in patents, both for the government and for the contractors operating with federal funding. It did not purport to grant either the contractor or the government an extraordinary power to strip independently existing rights of third parties.

2. Nor did the Bayh-Dole Act effect a profound revision of the Patent Act. In particular, it did not alter the law that provides that inventors, not their employers (including federal contractors), are the original owners of their inventions. And it most certainly did not, as the United States urges, subordinate the inventor's original right in his or her invention to the government or to the entities receiving government funding. U.S. Br. 13.

This is because the Act did not statutorily assign original title in inventions made with federal funding directly to contractors, instead of inventors. Instead, the Act's provisions presuppose that a contractor could come into possession of title to an invention (without specifying how), and explicitly provide the rules and obligations under which contractors can thereafter "retain" that title if the invention was supported with federal funds. 35 U.S.C. § 202(a). Because the Bayh-Dole Act does not specify any mechanism by which the contractor would first come into possession of the title that the Act allows it to "retain," the contractor's title would logically flow, under normal patent law principles, from an event

that occurred after the original title vested in the inventors when the invention was made.

As Respondent correctly notes, Resp. Br. 15, 22, the use of the word "retain" indicates that Congress recognized the necessity of a prior transfer from the inventor of his rights in the invention. The natural meaning of "retain" compels the conclusion that this provision refers to rights in inventions that have been previously transferred.

The Act uses similar language to explain that the government, pursuant to a funding agreement, "may receive title" to a subject invention where the contracting institution does not affirmatively act. 35 U.S.C. § 202(c)(1)-(3). Neither party, however, is given the right by the Act to "take" title from the inventor, nor does the Act speak of "vesting" title in inventions that have been made by the contractor's inventors or other individuals who are not a party to the funding agreement.

3. Respondent rightly focuses attention on the phrase "invention of the contractor" in § 201(e) to show that Congress assumed that the contractor had independently acquired the actual inventor's rights. A "subject invention" is an invention that was (a) conceived or first actually reduced to practice[3] with federal funds, and that is (b) "an invention *of the*

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[3] Conception of an invention is complete "when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation." *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994). An actual reduction to practice of an invention "requires that the claimed invention work for its intended purpose." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986). It is "[c]onception [that] is the touchstone of inventorship." *Burroughs Wellcome*, 40 F.3d at 1227.

contractor."[4] *Id.* § 201(e) (emphasis added). Under Petitioner's theory, federal funding is by itself the trigger that makes ownership of an invention vest in the contractor. That theory renders the phrase "invention of the contractor" mere surplusage in defining "subject invention," for if spending federal money alone were enough to make an invention the contractor's, then there would be no reason to require that it also be "an invention of the contractor." But the phrase "an invention of the contractor" can be given effect separate from federal funding by simply giving consequence to the well-established principle that the inventor is the original owner of her invention. In other words, the phrase "invention of the contractor" necessarily assumes an act which transfers ownership of the federally-funded conception or first actual reduction to practice from the inventors who make inventions to the contractor. A construction that fails to give effect to every clause and word where such is possible should be avoided. *Duncan* v. *Walker*, 533 U.S. 167, 174 (2001) ("'It is our duty "to give effect, if possible, to every clause and word of a statute."'").

4. Interpreting the Bayh-Dole Act to provide for an automatic vesting of title to an invention made with federal funding in the government or its contractor would also read out of the statute at least one critical section, contrary to the cardinal maxim that a statute is read, where possible, to give effect to all its parts. *FDA* v. *Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000). Specifically, 35 U.S.C. § 202(d) states that the government can grant requests for

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[4] Because the contractor is a nonprofit organization or small business, and because only natural persons can be inventors, the phrase "of the contractor" must mean "owned by the contractor," not "invented by the contractor."

"retention of rights by the inventor" where the contractor does not elect to retain title. 35 U.S.C. § 202(d). If the inventor never had title to his invention, as Petitioner posits, because title automatically vested in the contractor, then the language used in this portion of the statute would not make sense. Instead, the natural meaning of the words used in this clause reveal that the inventor must have necessarily had possession of title to his invention at a time prior to the point in time when title will be transferred to the government or the contractor. In other words, this clause is also perfectly consistent with the well-established principle that the inventor is the original owner of her invention.[5]

5. Contrary to the United States' position, U.S. Br. 21, 35 U.S.C. § 210 is not a provision of the Act that changed the provisions of the Patent Act that govern original ownership in inventions, including those made with some degree of federal funding. As § 210 provides by its express terms, the Bayh-Dole

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[5] Interpreting the Bayh-Dole Act to provide for an automatic vesting of title to an invention made with federal funding would also conflict with 35 U.S.C. § 202(e) that implicitly recognizes the ownership right of inventors. Under that provision, "when a Federal employee is a coinventor of any invention made with a nonprofit organization ... the Federal agency employing such coinventor may, for the purpose of consolidating rights in the invention ... license or assign whatever rights it *may acquire* in the subject invention to the nonprofit organization." 35 U.S.C. § 202(e)(1) (emphasis added). If the Bayh-Dole Act was a title vesting statute, as Petitioner urges, then there would be no need to "consolidate rights." Moreover, this provision explicitly recognizes cases in which inventorship rights dictate that rights under the Bayh-Dole Act are not exclusive to the contractor – as in this case. In the normal course of business, the federal agency would acquire its rights to the invention by an employment agreement and assignment.

provisions, which form Chapter 18 of the Patent Act, are to have precedence over "any other Act" (*i.e.*, acts other than title 35, United States Code) that govern the disposition of rights in inventions made with federal funding. The phrase "any other" in § 210 plainly is referring to portions of the United States Code other than the Patent Act that regulated the government ownership interests in inventions. And given that one purpose of § 210 was to make uniform a heterogeneous collection of such laws, it is logical that § 210 enumerates these other Acts that provide for government interests in inventions (i.e., provisions in 7 U.S.C., 30 U.S.C., 42 U.S.C., 50 U.S.C., 22 U.S.C., and 15 U.S.C.). Without this clarification, these other Acts of Congress could have frustrated the objective of the Bayh-Dole Act to establish a uniform federal policy governing disposition of the ownership interests of the government in inventions supported by federal funding.

The Bayh-Dole Act accordingly sought only to set up a simplified and unified contract-based system for transferring rights existing in inventions between the government and its funded contractors.[6]

6. Section 202, which speaks to "Disposition of rights" in a "subject invention," does not speak to rights in a patent[7], much less "vesting" of title in a

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[6] And as Respondents note, Congress specifically referred to vesting title when the procedure was different than that provided by Title 35 of the U.S. Code. Resp. Br. 23. Moreover, when it did so, Congress thought it important to particularly enumerate the procedures to follow. *Id.* at 23-24. That the Bayh-Dole Act does neither, even though displacing those acts, is equally consistent with an inference of no vesting and vesting. Pet. Br. 35.

[7] A "subject invention" is not a patent or even necessarily "a patentable invention" (though it might be), but rather simply

patent with contractors, whether "presumptively" or by "automatic[]" transfer of title from an inventor. Pet. Br. 26; U.S. Br. 18, 21, 26. It did not because the Patent Act, of which the Bayh-Dole Act is a part, already addresses vesting and transfer of patent title in explicit detail.

In particular, 35 U.S.C. § 101 provides that "whoever invents" an invention eligible for patent protection is entitled to receive a patent. The inventors – that is to say, the natural person or persons who made the invention – are the individuals specified in the statute who must then file a patent application to secure the patent.[8] *See id.* § 111. Once the patent is granted, title to that property right initially vests in the inventor or inventors, *i.e.*, the patentee(s). *Id.* §§ 151, 261. 35 U.S.C. § 261 then provides that the property interest may be disposed of through assignments from the "applicant" or the "patentee." Thus title can pass from the inventor to a successor-in-interest by a written conveyance, and

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"any invention ... conceived or first actually reduced to practice in the performance of work under a funding agreement." 35 U.S.C. § 201(e). There are of course many more requirements for an "invention" to be patentable. *See id.* §§ 101, 112, 102, 103.

[8] This of course derives from the fact that the U.S. Constitution provides the government with the power "[t]o promote the Progress of Science and useful Arts by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. Const. art. I, § 8, cl. 8. Thus people, not corporations are granted patents. Section 118 of the Patent Act allows a few exceptions to the general rule that applications must be filed by inventors. If an inventor cannot be located, or refuses to perform his contractual obligation to assign an invention to his employer, then the employer may file in place of the inventor, but even then the patent issues listing the name of the person(s) who are the inventor(s).

can do so immediately after it is established.[9] *Waterman* v. *Mackenzie*, 138 U.S. 252, 255 (1891); see also 35 U.S.C. § 100(d) ("'patentee' includes not only the patentee to whom the patent was issued but also the successors in title to the patentee.").

Of course, if a formal assignment has not been made, this Court has recognized that contract law can nevertheless require that result. *Solomons* v. *United States*, 137 U.S. 342, 346-48 (1890). Thus, where a contractor is entitled to, but fails to secure an assignment from an inventor before the inventor subsequently conveys rights in the patent covering a "subject invention" to a third party, specific performance can compel a transfer of the ownership of the patent property right. See *Fenn* v. *Yale Univ.*, 2005 WL 327138, at *6 (D. Conn. Feb. 8, 2005) (unpublished decision ordering inventor to assign patent obtained by breach of employment contract requiring assignment to university); see also *Fenn* v. *Yale Univ.*, 283 F. Supp. 2d 615, 625-28, 631, 640 (D. Conn. 2003) (detailing employment contract with assignment requirements and inventors breach).

The possibility of finding a basis in contract to compel the transfer of title, however, does not suggest that the Bayh-Dole Act itself changed the predicate event of vesting initial ownership of a patented invention in the inventors. Nor is such an

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[9] 35 U.S.C. § 152 provides that a patent can be granted to an assignee of the inventor, but only upon application made and sworn to by the inventor. In other words, a conveyance by the inventor is required whenever transfer of ownership is involved. *See also* George T. Curtis, *A Treatise on the Law of Patents* § 170 (4th ed. 1873) ("[T]he legal title to an invention can pass to another only by a conveyance which operates upon the thing invented after it has become capable of being made the subject of an application for a patent.")

interpretation of the Act necessary since contract law is more than capable of providing a remedy if an inventor acts outside the boundaries of commitments that individual has previously accepted by assigning his interests in the invention to another.

7. To be sure, the Bayh-Dole Act does provide blanket permission for recipients of federally-funded research, who elect to retain rights in the "subject invention," to procure patents on those inventions, thereby protecting the government's interest as well as the recipient's. 35 U.S.C. § 202(c)(3). However, that authority did not obviate the need to follow the statutory mandate that the individuals who are the "inventors" of the subject invention file the patent application in their name. Nor did it *sub silentio* remove the requirement of obtaining an assignment of title from the inventors in that application to effect the transfer in ownership of the patent application (and any patent that may issue on that application) for the invention that arose from the federal funding the employer received.

Indeed, the implementing regulations of the Bayh-Dole Act make clear that the federal funding agency expects the university to use written agreements that bind its employees to ensure the government interests in the patent applications are properly protected under existing statutory requirements. In particular, 37 C.F.R. § 401.14(f) specifies that:

> *Contractor* Action to Protect the Government's Interest.
>
> ....
>
> (2) The *contractor* agrees to require, by written agreement, its employees, other than clerical and nontechnical employees, to disclose promptly in writing to personnel identified as

> responsible for the administration of patent matters and in a format suggested by the *contractor* each subject invention made under *contract* in order that the *contractor* can comply with the disclosure provisions of paragraph (c), above, and to execute all papers necessary to file patent applications on subject inventions and to establish the government's rights in the subject inventions.[10]

Rule 401.14(f) thus establishes a contractual obligation under which the contractor agrees to safeguard the government's interest through written agreements with its inventors. And, consistent with provisions of the Patent Act, apart from the Bayh-Dole Act, these written agreements first require the inventors to file the patent application in their own names, to include the required oath or declaration as to their inventorship of the invention, and to assign their ownership rights to their employer either during the patenting process[11] or thereafter.

This is precisely what many agencies informed the public was the process for perfecting the government's interest in patents on inventions made with federal funding. For example, the National Institutes of Health in a public notice stated:

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[10] That the implementing regulations touched on the inventor's responsibilities rather than the Act is not unusual since the Act was not directed to title and given that this was how prior agencies made express provisions for the disposition of title to patents. *See, e.g.*, 45 C.F.R. § 650.4(b) (1977) (providing that the National Science Foundation would "determine the disposition of the invention [made under the grant] and title to and rights under any patent application.")

[11] As this Court long-ago recognized, "[i]nventions may be assigned before they are patented." *Cammeyer* v. *Newton*, 94 U.S. 225, 226 (1876).

> The Bayh-Dole Act requires that there be employee agreements in place at the awardee organizations that obligate inventors to assign title to Federally-supported inventions to the organization.

24 NIH Guide, No. 33, *A "20-20" View Of Invention Reporting To The National Institutes Of Health* (Sept. 22, 1995), *available at* http://grants.nih.gov/grants/guide/notice-files/not95-003.html (answer to question 17 "What happens to an invention when the inventor/principal investigator transfers to a new institution?")[12]

8. It also is abundantly clear, based on past practices, that universities have historically recognized and accepted that they must first obtain title to subject inventions from their inventors, and that they do not receive that title automatically simply by operation of the Bayh-Dole Act. Universities consistently require their inventors to execute assignments as to "subject inventions" made by those inventors, no later than by the time the inventors file their patent applications, as part of the invention disclosure process and/or as part of their conditions of employment. See, *e.g.*, Resp. Br. 34 (citing university policies concerning assignment); *id.* at 34-35 (citing Stanford assignment of the patents at issue); *Fenn*, 283 F. Supp. 2d at 621-22, 628 (pre- and post-Bayh-Dole inventor assignment policy of Yale for patents covering inventions obtained with the aid of federal funds); *Regents of Univ. of N.M.* v. *Knight*, 321 F.3d

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[12] This agency further noted that, where the inventor leaves the contracting organization, then either the inventor or the organization, with agency permission, may transfer rights to the new organization to which the inventor moves. 24 NIH Guide, *supra*.

1111, 1114-15, 1118-19 (Fed. Cir. 2003) (post-Bayh-Dole UNM faculty assignment of patents to UNM covering inventions made at a funded laboratory); *Univ. of Pittsburgh* v. *Townsend*, 542 F.3d 513, 517-18 (6th Cir. 2008) (post-Bayh-Dole inventor assignment policy of University of Pittsburgh for patents covering inventions obtained from government-sponsored research grants). And for the past 30 years, without reading the Act as automatically vesting title in inventions arising from federally-funded research, research has thrived and inventions made with federal funding have successfully been brought to market.

Indeed, the argument now advanced by Petitioner and the United States is as new to the universities as it is to BIO. It affects everyone's settled expectations, with no clear benefits to anyone, except Stanford University in this particular case. In fact, as explained below, Petitioner's interpretation will have severe detrimental effects. Thus, Petitioner's attempt to have this Court rewrite history and the statute, effectively relieving it and other contractors from their obligations to secure clear title to federally-funded inventions and control the conduct of their employees, should be rejected.

Understandably, universities may prefer to not be burdened with the obligation of regulating the conduct of their researchers in connection with securing title to inventions made by those researchers or in monitoring interactions of those researchers with third parties. That administrative burden, however, is not an unreasonable cost for universities to bear to perfect their interests in, and to thereby derive the economic benefit of, patents on inventions over which the university has a legitimate claim of ownership.

II. INTERPRETING THE STATUTE AS PETITIONER SUGGESTS WOULD DETER COLLABORATION BETWEEN PRIVATE INDUSTRY AND CONTRACTORS

1. Many biotech inventions are the product of collaborative efforts. *See, e.g.*, Eisenberg, *supra*, at 1671 (noting that in biomedical research fields, researchers in government, university and commercial laboratories often work collaboratively on the same problems.) Such joint work allows for shared costs, shared risks, shared facilities, and shared expertise. Given the numerous benefits to society that these collaborations yield – including both advancements in scientific knowledge and understanding as well as tangible products and services that benefit patients – collaborations plainly should be encouraged.

Collaborations require that both parties to the collaboration see individual and mutual benefits from the collaboration. For the biotechnology industry, investment in collaborative research and development is predicated on – and motivated by – an expected return on investment in the form of marketable products that are protected by patents whose ownership is clear and ascertainable. Legal certainty, in the form of clear rules of patent ownership, is one of the many necessary conditions that must be met before biotechnology companies and their investors are willing to engage in the high-cost, high-risk endeavor of developing a biotechnology product from its inception through clinical trials to regulatory approval.

Petitioner's interpretation of the Bayh-Dole Act would establish a regime under which companies that help to make an invention in collaboration with a nonprofit research institution will face far greater

uncertainty as to whether their financial and inventive contribution will result in ownership interests in patents on inventions arising from those collaborations.

When companies can neither predict nor control the results of their investments, they understandably tend to be less likely to engage in related research and development. *See* Wendy H. Schacht, CRS Rep. RL32076, *The Bayh-Dole Act: Selected Issues in Patent Policy and the Commercialization of Technology* CRS-14 (Dec. 8, 2006). Under the arrangements that have existed for decades, private third parties have cooperated with universities to the benefit of both parties and the public. The Court should be quite cautious in construing the Bayh-Dole Act in a way that would undermine the positive collaborations that have developed during the past 30 years.

2. Petitioner asserts that their rule provides the "clarity" necessary to benefit collaboration and encourage technological development. *See* Pet. Br. 45-48, 52-53. But Petitioner's unprecedented proposition that original ownership of an invention can be divorced from inventorship, far from contributing to legal certainty in the life sciences, will call into question prior agreements that relied on longstanding existing ownership law and will discourage industry from collaborating with universities (or other "contractors").

Petitioner's rule will create new uncertainties where conception and actual reduction to practice occur at separate institutions, where there is joint invention, and anytime multiple federal grants are involved. It will also call into question those collaborative agreements where the private-industry participant bargained for an allocation of rights as a

condition of entering into the collaboration, sharing technology and other know-how and providing economic support.

3. Under Petitioner's interpretation, if a conception or a first actual reduction to practice was made under a federal grant, then the grantee, *e.g.*, university, automatically gains title. This rule will create particularly inequitable situations in the biotechnology setting.

Biotechnology companies often are able to conceive of a new therapeutic invention without conducting clinical testing of the agent. For example, the company's researchers may identify a new agent, test it in sophisticated animal and laboratory models, and thereby verify that it is a promising agent for use in human treatment. Even though the company may not have established that the invention will achieve therapeutic results in humans, it would nevertheless be appropriate for the company to file a patent application at this stage of development. See *Burroughs Wellcome Co.* v. *Barr Labs., Inc.*, 40 F.3d 1223, 1228-30 (Fed. Cir. 1994). That filing would constitute, at a minimum, a "constructive" reduction to practice of the invention. *Id.*

Development, of course, does not stop at this point. Instead, companies often partner with university hospitals to conduct proof-of-concept clinical testing in humans of their new agent. These proof-of-concept clinical trials may constitute the first "actual" reduction to practice of the invention in humans, though they require only ordinary skill to carry out. Where such clinical studies merely confirm the operability of the invention that was fully conceived previously, they do not provide any inventive contribution and are neither necessary to obtain a patent nor entitle the clinical investigators to co-

inventorship, *id.* at 1228, 1230, or presumptive co-ownership, *Ethicon, Inc.* v. *U.S. Surgical Corp.*, 135 F.3d 1456, 1465 (Fed. Cir. 1998).

Of course, university laboratories are often selected because of a particular expertise they possess through their ongoing clinical research activities. Invariably, those activities enjoy some degree of federal funding.

Under Petitioner's theory, whereby a contractor's ownership interest vests either at the point of conception or the first actual reduction to practice of the invention, the university laboratories could claim an ownership interest in the invention by performing an act *after* the invention was otherwise "invented" by employees of the private company.

That scenario would create endless conflicts and uncertainty in industry and in a process that is already subject to tremendous risks and challenges. In particular, a business that planned its decade-long development of a new therapeutic product under well-accepted legal principles governing original ownership of an invention, would face unanticipated conflicts and risks of losing control of patent rights in technology it developed. Petitioner's interpretation could call into question many of these established agreements, to the great detriment of the industry.

4. The Patent Act provides that two or more persons may apply for a patent jointly. 35 U.S.C. § 116. Co-inventors are co-owners, each having an undivided right to do as she pleases with her interest in the invention without the consent of other co-owners. *Id.* § 262; see *Schering Corp.* v. *Roussel-UCLAF SA*, 104 F.3d 341, 344 (Fed. Cir. 1997). This right enables each co-inventor to be able to assign its ownership interest to its employer, even if it was in

advance of the invention being made. If patented inventions developed from federally-sponsored dollars include co-inventors from different establishments, it should be the case that each of those establishments should be entitled to control the disposition of the patent, provided assignments have been properly executed.

Petitioner's position is that use of federal monies subordinates inventors' rights, regardless of how many inventors there are. By that argument, it does not matter how many different inventive entities there are in a patented invention, the title vests automatically in just the entity that is funded.[13] Petitioner's rule could call into question any prior disposition of patent rights by co-inventors who were not part of the federally-funded institution.

5. An invention may be conceived jointly by researchers at two or three different federally-funded universities. And it may be first actually reduced to practice at yet another federally-funded institution. Not uncommonly, one or more of these institutions will be operating under separate funding agreements. Indeed, this is not an unrealistic scenario given that today's inventions often involve different branches of science, *e.g.*, biomedical advances often rely on electronics as well as the biological sciences.

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[13] *Amici* Association of American Universities et al. suggest that § 202(e) would prevent the Bayh-Dole Act from vesting ownership rights of co-inventors that were not working at the contractor who was federally-funded. Assoc. of Am. Univ. Br. 23. But the logic of Petitioner's argument does not guarantee that outcome. Petitioner's position is that use of federal monies subordinates inventor's rights and the logical extension of that argument is that it does not matter how many different inventors there are, the title vests in just the funded party automatically.

Petitioner's theory, where original title is divorced from the inventors and depends only on the federal grants under which investigators worked on the conception or first actual reduction to practice, could greatly dilute ownership – "vesting" each of the funded entities with an equal, and conflicting, claim to title to the invention. Thus, the ownership of such inventions would have no clear origin. And, because these ownership rights would not be traceable through written contracts, a potential licensee seeking assurances of clear title, would face an entirely new layer of uncertainty.

6. Private industry and public university collaborations are usually governed under detailed agreements that provide for an allocation of ownership rights in any inventions that may be made during the collaboration. The agreements may allocate rights based on the amount of, or importance of the know-how provided by one of the collaborators. However, under Petitioner's theory, despite these bargained-for rights, the university may end up with a superior ownership right to the inventions arising from the collaboration even if the contribution by the private company was clearly the most important contribution to achieving the invention.

The university may also end up with a superior ownership right in the clinical trial scenario discussed above, despite not having contributed at all to the conception of the invention. Such trials are often governed by collaboration agreements and the private company who is the patent owner, and whose employee(s) were the inventors, usually will not assign title in the invention simply to have the clinical trials carried out in a particular laboratory. However, under Petitioner's theory, notwithstanding the parties agreement, that would be the automatic

result where the university was carrying out proof-of-concept trials.

7. Petitioner's rule, cast as an absolute effect of the statute, would create uncertainty and/or chaos over existing industry ownership rights in inventions touched by federal funding. It would of course be devastating if a biotech company, after investing hundreds of millions of dollars in technology it assisted in developing, and subsequently patented, discovered that it did not have title to the underlying patent(s) despite otherwise valid assignments of the interests of its inventors to the company. Yet that result could ensue under Petitioner's theory where there was co-inventorship with a federally-funded contractor or where the federally-funded contractor sponsored proof-of-concept clinical trials. And such a result would certainly deter any future collaboration where federal monies were provided.

Petitioner's interpretation of the Act would also fundamentally disrupt the process by which the private sector and universities negotiate interests in patents arising from collaborative research. In particular, the rule advanced by the Petitioner would operate to unfairly discount both economic and intangible contributions of the private party in a collaboration, as it would, as a matter of law, cause an automatic vesting of ownership in any invention that enjoys any degree of support from federal funding. Such a rule will have the practical effect of discouraging collaborations that could yield useful inventions, as it removes the arms-length process of negotiating interests in the fruits of a collaboration.

In short, the environment that will result from this rule is the same environment that caused the private sector to avoid investing in development of federally-supported technology prior to the Bayh-Dole Act. The

statute was not adopted to be self-defeating, but that is precisely what Petitioner's and United States' interpretation will accomplish. There is no need to inflict this result in the biotechnology industry to deliver a solution dictated by one set of unique facts. Absent a clear statement from Congress requiring such upheaval, which simply does not exist, the Court should maintain the *status quo*, which has served the interests of all affected parties and the nation's economy well.

8. Petitioner, the United States, and several amici warn that the opinion below would create new uncertainties that would arise from "rogue" inventors who might have executed unknown prior assignments, casting a cloud of uncertainty over university-licensed patents, preventing universities from warranting clear title, and discouraging potential corporate licensees from investing in the licensed technology. Such fears are overstated. The supposed "new" risk of defective title is not new at all.

This risk, however remote, was always assumed to exist by in-licensing companies regardless of whether the would-be licensor is a private company, a federal contractor, or a university. That is why biotechnology companies routinely conduct extensive due diligence on the patent's chain of title, by seeking warranty of title from and other contractual remedies against the licensor; by relying on the protections of 35 U.S.C. § 261 (an unrecorded assignment is void against a subsequent purchaser for valuable consideration unless recorded in the U.S. Patent and Trademark Office within a specified time limit), and others. Thus, this risk has been managed as a routine business practice.

III. EQUITABLE AND CONTRACT REMEDIES ARE AVAILABLE WHERE INVENTORS ASSIGN RIGHTS TO INVENTIONS IN VIOLATION OF UNIVERSITY POLICIES, OR IN A MANNER INCONSISTENT WITH BAYH-DOLE

The Bayh-Dole Act allocates the rights and obligations between federal funding agencies and their contractors through use of funding agreements that bind both the agency and the contractor and its successors, assigns, and subcontractors. 35 U.S.C. § 202(c)(1)-(8); *Id.* § 201(b) (defining "funding agreement"). Because the inventor is typically neither a party to the funding agreement nor in privity with the funding agency, it is the contractor's responsebility to protect the government's interest by securing rights to the invention from the inventor through separate written instruments. See, *e.g.*, 24 NIH Guide, *supra*.

Universities and other nonprofit research institutions meet this obligation in a number of ways, such as by obtaining express assignments or obligations to assign inventions to them from their faculty; by binding their researchers to pervasive research policies that require them to comply with the conditions of extramural grant awards; or by patent and intellectual property policies that are incorporated in employee handbooks as a condition of employment. See, e.g., *Georgetown University Policy And Procedures For Inventions, Copyrights, Patents, and Technology Transfer* B.3-4 (1999), *available at* http://facultysenate.georgetown.edu/Archives/Patent IntelProp/intell-prop-policy1999.pdf.; Univ. of Minn., *Intellectual Property Policy* § IV subd. 2. (b), § VII (4) (1999), *available at* http://www1.umn.edu/usenate/policies/intelproperty.html; GAO Report to Cong.

Comms., GAO/RCED-98-126, *Technology Transfer Administration of the Bayh-Dole Act by Research Universities* 14 (May 1998) (noting that inventors at University of Wisconsin-Madison assign rights to its licensing foundation, WARF, under Bayh-Dole). Contractual obligations, whether express or implied, thus operate as the main constraint on the disposition of invention ownership rights by nonprofit federally-funded inventors. Additionally, such inventors may, in highly fact-specific situations, be under equitable obligations to their institutions that affect their ability to dispose of ownership rights in inventions made under federal support. For example, as an intended third-party beneficiary of the funding agreement, an inventor who knowingly accepts the benefits of the funding agreement through and from his institution could be deemed to be under an equitable obligation not to execute bad-faith assignments, or otherwise act in ways that are inconsistent with his institution's obligations to the government under that funding agreement. There is no reason why equitable relief, for example in the form of specific performance of an inventor's obligation to assign, or rescission of a bad-faith assignment to a third party that may have occurred, would not be available to give a nonprofit research institution the rights to which it is entitled and which it needs to safeguard the funding agency's interests.

Indeed, in instances where university-employed inventors have concealed valuable inventions from their institution, or assigned inventions in bad faith to third parties for personal gain, courts have recognized the availability of a number of equitable and contract remedies, including for breach of contract, breach of fiduciary duty, fraud, tortious interference, theft, unjust enrichment, and con-

version of property. See *St. John's Univ.* v. *Bolton*, 2010 WL 5093347, at *6-7 (E.D.N.Y. Dec. 10, 2010); *Fenn*, 283 F. Supp. 2d at 620, 640. Petitioner, their supporting amici, and the United States have provided no explanation why such time-tested remedies are so inadequate that the Bayh-Dole Act must be interpreted, in the absence of a clear statement from Congress, contrary to the Patent Act's fundamental principle that original ownership of inventions vests in inventors – not their employers.

This is not a case where the Federal Circuit's rule will deprive the government of any rights to inventions arising out of federal sponsorship, or deprive the public of technology arising from such funds, or impede collaborative efforts, or even deprive a university of ownership rights in federally-funded inventions. In other words, all of the issues the Bayh-Dole Act sought to correct from the prior government ownership of inventions regime, are left intact with that court's ruling. Written assignment of patent rights has been the norm for federally-sponsored research, for 30 years, even for Petitioner. And there is scant justification, if any at all, to change that paradigm.

CONCLUSION

For all of the foregoing reasons, Amicus respectfully requests this Court affirm the Federal Circuit's decision in this case because the Bayh-Dole Act does not automatically vest title in patents to contractors.

Respectfully submitted,

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AMICUS CURIAE BRIEF

No. 09-1159

IN THE

Supreme Court of the United States

BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY,
Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.,
Respondents.

On Writ Of Certiorari
To The United States Court Of Appeals
For The Federal Circuit

BRIEF OF INTEL CORPORATION, ELI LILLY AND COMPANY, JOHNSON & JOHNSON, LIFE TECHNOLOGIES CORPORATION, PFIZER INC., AND SAP AMERICA, INC. AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICI CURIAE*[1]

To better "promote collaboration between commercial concerns and . . . universities," Congress passed the Bayh-Dole Act. 35 U.S.C. § 200 *et seq.*

Amici curiae are a diverse group of companies that make semiconductors, software, pharmaceuticals, medical devices, biotechnology tools, and consumer products. Collectively, *amici* spend close to $30 billion annually on research and development, frequently collaborating with universities and small businesses in the development of new products and technologies. *Amici* collectively own tens of thousands of patents, which they rely upon to protect their substantial investments in research and development.

In their collaborations with universities and small businesses, *amici* use contracts to govern the distribution of intellectual property rights arising from those collaborations. This case presents the question whether a university that funds research

[1] Pursuant to this Court's Rule 37.3(a), letters of consent from all parties to the filing of this brief have been submitted to the Clerk. Pursuant to this Court's Rule 37.6, *amici* state that this brief was not authored in whole or in part by counsel for any party, and that no person or entity other than *amici* or their counsel made a monetary contribution intended to fund the preparation or submission of this brief.

with federal money may use the Bayh-Dole Act to nullify the patent rights of its industrial collaborator in a jointly developed invention. Petitioner's central contention is that the Bayh-Dole Act empowers a university to dispossess inventors and their assignees of all their rights in any invention that is made a "subject invention" under the Act, even if the government-funded university itself otherwise has no rights in that "subject invention."

Amici curiae have a substantial interest in the correct resolution of that contention because it will likely control the nature and extent of their future collaborations with universities and their employees and students. Moreover, because Executive Order No. 12,591 purports to extend the Bayh-Dole regime to a wide range of government contractors, this Court's resolution of the question presented could impact *amici*'s ability to collaborate with virtually any recipient of government funding (or any of its employees).

If petitioner's interpretation of the Bayh-Dole Act is adopted by this Court, the Act will discourage the research collaborations it was intended to foster. Petitioner's interpretation of the Act leaves an industrial collaborator with few means to protect its inventive contributions from seizure. And, as explained *infra*, even a firm that bars the door to any would-be collaborators could still find its intellectual property jeopardized by petitioner's interpretation of the Act.

STATEMENT

The critical facts, undisputed in this Court, are:

At all pertinent times, the named inventors of the patents-in-suit were employed by Stanford and

were part of a team conducting research into means of detecting HIV, the virus that causes AIDS. That team, led by Dr. Thomas Merigan, determined that a groundbreaking biochemistry technique—the polymerase chain reaction ("PCR")—might have implications for its research. The PCR technique had been developed by scientists at Cetus Corporation in the mid-1980s. Merigan arranged for his colleague Dr. Mark Holodniy, who had no experience with PCR techniques, to conduct research at Cetus, where Merigan was on the scientific advisory board. Pet. App. 17a, 31a, 34a-35a.

As a condition to gaining access to Cetus and its proprietary information, Holodniy signed a Visitor Confidentiality Agreement ("VCA") that assigned to Cetus Holodniy's "right, title, and interest" in any invention made "as a consequence of [his] access" to Cetus facilities. Pet. App. 35a-36a (quoting VCA). Although Holodniy previously had agreed to assign (at some unspecified future date) his rights in inventions made in the scope of his employment at Stanford, he had not, at the time he assigned his rights to Cetus, actually assigned any such rights to Stanford. *Id.* at 13a-14a. Merigan and Stanford had at least constructive knowledge of Holodniy's assignment of his rights to Cetus. *Id.* at 16a-17a, 64a. Indeed, Stanford negotiated other collaborative agreements with Cetus, but none of those agreements specifically addressed the activities of Holodniy. *See id.* at 4a-5a, 17a, 33a.

Holodniy worked at Cetus for nine months in 1989. During the time he worked at Cetus, Holodniy conceived the patented invention at issue in this litigation. Pet. App. 56a-57a. Both courts below found—and it is not disputed here—that the inven-

tions at issue arose "as a consequence of" Holodniy's access to Cetus, triggering Holodniy's assignment to Cetus. *Id.* at 15a, 64a-65a.

Holodniy returned to Stanford. At some point, Stanford began funding Dr. Merigan's clinical research on use of PCR as an HIV diagnostic tool with federal funds.[2] With the assistance of those federal funds, Holodniy employed the knowledge he gained at Cetus and, working with two others, reduced the invention conceived at Cetus to practice.

Unbeknownst to Cetus, Stanford filed patent applications for the invention in 1992, eventually naming Holodniy as one of four inventors. Pet. App. 5a, 40a. Stanford claimed that the invention was a "subject invention" under the Bayh-Dole Act, based on its assertion that the invention had been reduced to practice with the assistance of federal funds, and notified the government in April 1995 that it was electing to "retain title" to the invention conceived at Cetus and assigned by Holodniy to Cetus. *Id.* at 5a-6a. Holodniy did not assign his rights in the invention to Stanford until May 1995—six years after he had assigned those rights to Cetus. *Id.* at 14a, 19a.

But for the fact that Stanford funded Merigan's research with money from the federal government, there would be no question that Stanford and Cetus's

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[2] In this Court, Stanford claims that the government funding for Merigan's research began before Holodniy joined Merigan's lab in 1988. Pet. Br. 17. But Stanford's briefing below suggests that the federal funding began in July 1990—eight months after Holodniy returned to Stanford from Cetus and long after the invention had been conceived there. Stanford C.A. Reply Br. 43 (referring to "federally funded clinical research at Stanford beginning in July 1990").

successor-in-interest Roche are co-owners of the invention. *See* Pet. App. 27a-28a. Yet Stanford contends that because it made a unilateral decision to underwrite Merigan's research with federal funds (on its earlier telling, after the invention was conceived at Cetus), the Bayh-Dole Act governs the distribution of patent rights. Under that Act, Stanford argues, its unilateral election to "retain title" to the invention retroactively voided Holodniy's otherwise valid prior assignment to Cetus, divested its collaborator of any interest in the invention, and arrogated that interest to itself.

The Federal Circuit was "unconvinced of Stanford's interpretation of the Bayh-Dole Act." Pet. App. 19a. It found no "authorities or reasons" adequate to explain why "election of title under the Bayh-Dole Act had the power to void any prior, otherwise valid assignments of patent rights." *Ibid.* If the Act did "not automatically void ab initio the inventors' rights in government-funded inventions," the panel could find "no reason why the Act voids prior contractual transfers of rights." *Id.* at 19a-20a.

SUMMARY OF ARGUMENT

According to Stanford and the government, the Bayh-Dole Act empowers a university to dispossess inventors and their assignees of all their rights in any invention conceived or first actually reduced to practice using federal funds. This interpretation of the Act, however, cannot be squared with the plain text of the Act or the agency regulations implementing it. Nor can it be squared with the Act's central purpose: to promote collaboration between industry and academia.

I. The Bayh-Dole Act does not diminish inventors' rights in their inventions. Consistent with the Constitution's authorization to Congress to award patents to "Inventors," it has been well established since the Founding that patent rights vest initially in the inventor. On the rare occasions when Congress has departed from this principle, it has done so explicitly. But nowhere does the Bayh-Dole Act explicitly divest inventors of the rights in their inventions.

To the contrary, the text of the Act makes plain that it applies only to inventions in which a contractor such as a university already has acquired rights. The Act governs the disposition of rights only in "subject invention[s]," 35 U.S.C. § 202(a), which the Act defines as "any invention *of the contractor* conceived or first actually reduced to practice in the performance of work under a funding agreement," *id.* § 201(e) (emphasis added). The phrase "invention of the contractor" can mean only an invention in which the contractor already has acquired rights, for only then could the invention properly be said to be an invention *of the contractor*.

The text of the Act also makes plain that it does not empower a university to seize rights in an invention in which it previously had none. Under the Act, universities may "elect to retain title to any subject invention." 35 U.S.C. § 202(a). But a university cannot sensibly elect "to retain" that which it has not yet received.

That the Act does not diminish inventors' rights in their inventions is reflected in the Department of Commerce's regulations. By instructing all contractors "to require, by written agreement," their technical employees "to execute all papers necessary . . . to establish the government's rights in the subject in-

ventions," 37 C.F.R. § 401.14(f)(2), the Department's regulations presume that inventors will initially possess the rights in their inventions, and that a university will secure patent rights by traditional contract with inventors.

Nor does the historical background of the Bayh-Dole Act support Stanford's and the government's effort to read traditional inventorship and assignment rights out of the Bayh-Dole regime. While it is true that Congress intended the Act to bring uniformity to the mélange of preexisting agency policies on patent rights, there is nothing in the Act's history to suggest that Congress intended to achieve such uniformity by empowering universities to divest inventors and assignees of all rights in inventions created with the assistance of federal funding. The far more reasonable inference to be drawn from the Act's history is that Congress meant to preserve the fundamental principle that all rights in a patent originate in the inventor and pass only by assignment.

II. The Bayh-Dole Act was intended "to promote collaboration between commercial concerns and nonprofit organizations, including universities." 35 U.S.C. § 200. But Stanford's interpretation of the Bayh-Dole Act threatens the very collaboration the Act was intended to foster.

Indeed, Stanford's novel interpretation of the Act would discourage collaboration by allowing universities and other contractors to engage in predatory behavior. Under Stanford's view, for example, a university could attempt to escape its contractual obligations and terminate a commercial collaborator's rights in an invention simply by sprinkling the research project with a modest amount of federal funds. What is more, a company could be stripped of

its rights in an invention even if it had not entered into a collaboration at all: An employee could conceive an invention at a company, assign all rights in the invention to the company, and then decamp to a university and there actually reduce the invention to practice with federal funds. On Stanford's and the government's view, the *post hoc* federal funding nullifies any previous contractual assignment.

Congress could not have intended the Bayh-Dole Act to generate such unsettling and disquieting results. The practical effect of Stanford's and the government's interpretation is to place the burden on commercial partners to monitor not only their own employees but also those of the university, in order to ensure that the company's rights in an invention are not threatened by the expenditure of federal money. This, manifestly, is not what Congress intended, for it would inevitably chill the very collaboration the Act was meant to foster.

ARGUMENT

I. THE BAYH-DOLE ACT DOES NOT DIMINISH INVENTORS' RIGHTS IN THEIR INVENTIONS.

A. All Rights In A Patent Originate In The Inventor And Pass Only By Assignment.

Article I of the Constitution empowers Congress "[t]o promote the Progress of Science and useful Arts, by securing . . . to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. Const. art. I, § 8, cl. 8. The first Congress exercised this authority by enacting the Patent Act of 1790. That Act provided "[t]hat upon the petition of any person or persons . . . setting forth, that he, she, or they, hath or have invented or discovered" an in-

vention, a patent could be granted to "such petitioner or petitioners," *i.e.*, the inventors, or "their heirs, administrators or assigns." Act of Apr. 10, 1790, ch. 7, § 1, 1 Stat. 109, 109-10.

The law today remains substantially the same: The applicant must affirm that "he believes himself to be the original and first inventor of the [invention] for which he solicits a patent," 35 U.S.C. § 115, and patents may be issued only to the applying inventor or inventors, *id.* § 151, or an assignee, *id.* § 152, and are "assignable in law by an instrument in writing," *id.* § 261.

Thus, for 220 years, consistent with the constitutional prescription that the "exclusive Right" of a patent be "secur[ed]" to "Inventors," our patent laws generally have conferred all patent rights in an invention, in the first instance, in its human inventor or inventors: "whatever invention he may thus conceive and perfect *is his individual property.*" *Solomons v. United States*, 137 U.S. 342, 346 (1890) (emphasis added). *See also Hapgood v. Hewitt*, 119 U.S. 226, 233 (1886). Today, the leading commentator on patent law describes this foundational fact of patent-law life thusly: "The presumptive owner of the property right in a patentable invention is the single human inventor, in the case of a sole invention, or the several human inventors, in the case of a joint invention." 8 Donald S. Chisum, *Chisum on Patents* § 22.01 (2009). Indeed, the principle that patent rights originate in the inventor is so well-established that even the government does not dispute it. *Amicus* Brief of United States 21 ("the right to obtain a patent on an invention generally belongs to the inventor"); *see also Manual of Patent Examining Procedure* § 301 (8th ed. 2010) ("The ownership of the

patent (or the application for the patent) initially vests in the named inventors of the invention of the patent.").

It is just as well established that all subsequent patent ownership flows from the inventor through written assignments. 35 U.S.C. § 261. Indeed, this Court has held that "title to [a patent] can pass *only* by assignment." *United States v. Dubilier Condenser Corp.*, 289 U.S. 178, 187 (1933) (emphasis added); *see also* 8 Chisum, *supra*, § 22.01 ("[t]he inventor or inventors may then transfer ownership interests by written assignment to anyone (including a corporation or other entity)"). Thus, in the ordinary course, a university can acquire inventions by its employees only through contractual relationships. *Dubilier*, 289 U.S. at 187 ("The respective rights and obligations of employer and employee, touching an invention conceived by the latter, spring from the contract of employment."). Where there is no employment contract, or where the contract does not expressly cover inventions, this Court has made clear that such rights in an invention remain in the inventing employee. *Id.*; *see also Solomons*, 137 U.S. at 346.[3]

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[3] The government invokes Executive Order No. 10,096 to argue that the "government may allocate rights in inventions made by its employees." *Amicus* Brief of United States 23 n.3. But Executive Order No. 10,096 is premised on statutes authorizing the government to directly regulate its employees. *See Heinemann v. United States*, 796 F.2d 451, 455-56 (Fed. Cir. 1986). That authority is inapplicable here.

B. The Bayh-Dole Act Did Not Alter The Foundational Principle That Patent Rights Vest Initially In The Inventor.

Stanford contends that the Bayh-Dole Act divests inventors and their assignees of any rights in inventions made "subject inventions" by dint of the contractor's use of federal funding. *See, e.g.*, Pet. Br. 30; *Amicus* Brief of United States 6. But "Congress . . . does not alter the fundamental details of a regulatory scheme in vague terms or ancillary provisions—it does not, one might say, hide elephants in mouseholes." *Whitman v. Am. Trucking Ass'ns*, 531 U.S. 457, 468 (2001). Accordingly, on the rare occasions when Congress has altered the fundamental patent-law principle that patent rights accrue in the inventor, it has done so explicitly.

For example, when Congress determined that certain inventions created under NASA contracts should "be the exclusive property of the United States," it used that explicit language and further provided that the patent "shall be issued to the United States upon application made by the Administrator." 42 U.S.C. § 2457(a). Similarly, in the copyright area, when Congress wanted to vest copyrights in an author's employer rather than the author, Congress enacted a statute with express language to effectuate that result. 17 U.S.C. § 201(b).[4]

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[4] Under the Copyright Act, copyright in a work generally "vests initially in the author," 17 U.S.C. § 201(a), but "[i]n the case of a work made for hire, the employer . . . is considered the author," *id.* § 201(b). No similar language, declaring universities to be inventors, appears in the Bayh-Dole Act.

Stanford and its *amici* point to no comparably explicit language in the Bayh-Dole Act divesting inventors of their rights in their inventions because there is none. The Act contains no bar on inventors acquiring rights in inventions. Nor does the Act contain language that vests patent rights in any non-inventor. To the contrary, the statutory text, the governing regulations promulgated by the agency charged with the statute's administration, and the historical circumstances leading to the statute's enactment all point to the conclusion that the Act applies only to inventions previously assigned to the contractor by the inventor.

1. The text of the Act makes plain that it applies only to inventions in which a contractor already has rights and does not empower the contractor to seize rights in an invention in which it previously had none.

The Bayh-Dole Act governs the disposition of rights only in "subject invention[s]." 35 U.S.C. § 202(a). Section 201 of the Act defines "subject invention" as "any invention *of the contractor* conceived or first actually reduced to practice in the performance of work under a funding agreement." *Id.* § 201(e) (emphasis added). Because only a human being can be an inventor, the possessive phrase "invention of the contractor"—synonymous with "contractor's invention"—can mean only an invention in which the contractor already has acquired rights. Only then could the invention properly be said to be the "contractor's invention."

Yet Stanford argues that "invention of the contractor" is "naturally read" to include "all inventions made by the contractor's employees." Pet. Br. 32. That supposedly "natural[] read[ing]" of the statute

flatly contradicts this Court's precedents, which have long made clear that, absent a valid written assignment, an invention created by an employee is *not* the employer's invention.

In *Dubilier*, which neither Stanford nor the United States cites in their opening briefs, the inventors were government employees who devised and patented an invention during the course of their employment with the government. *See* 289 U.S. at 185. The government sued the inventing employees' exclusive licensee for ownership in the patents, arguing that the invention should be the property of the employer when it was made by an "employee . . . hired for the purpose of doing inventive work in a particular field." *Id.* at 180 (Arg. for the U.S.). This Court rejected the government's argument, holding that "the contract of employment" determines "[t]he respective rights and obligations of employer and employee" in any invention, *id.* at 187, and that in the absence of some provision addressing the employer's rights in the employee's inventions, there could be no "implication of any agreement to assign their inventions or patents," *id.* at 196. The inventions and patents, therefore, belonged to the inventors and not to their employers. *Ibid.*; *see also Solomons*, 137 U.S. at 346 ("nor does the mere fact that an inventor is at the time of his invention in the employ of the government transfer to it any title to, or interest in it"). Against this background—constant rejection of employers' assertions that employers own the inventions of their employees (even when the employer was the United States)—Stanford's indistinguishable assertion that "invention of the contractor" is "naturally read" to mean "inventions made by the contractor's employees" is baffling.

Stanford's and the government's interpretation of the statutory phrase, "elect to retain title," as "an affirmative grant of title" (Pet. Br. 36)—is equally puzzling. The Act's election provision does not offer contractors the windfall opportunity to acquire an ownership interest in an invention in which it previously had none. When used with an object such as property, money, or title, the authoritative dictionary in use at the time of the Bayh-Dole Act's enactment defined the verb "retain" as "to hold or continue to hold in possession or use; continue to have, use, recognize, or accept." *Webster's Third New Int'l Dictionary* 1938 (1976); *see also Webster's Second New Int'l Dictionary* 2126 (1954) (same); *Union Commerce Bank v. Comm'r*, 339 F.2d 163, 167 (6th Cir. 1964) ("we can only say that the construction of the word 'retained' offered by petitioner . . . is not the customary definition. Webster defines 'retain' with such synonyms as 'keep,' 'hold,' 'to hold in possession or use'") (footnote omitted).

One cannot sensibly elect to "continue to hold in possession" that which he has not yet received. If Stanford were correct and "§ 202(a) operates as an affirmative grant of title," then Section 202(a) provides not an election "to *retain* title" but an election to *obtain* title. And contrary to Stanford's view (Pet. Br. 36), the Bayh-Dole Act's reference elsewhere in the Act to a contractor that has "acquired title" or "receives title" hardly demonstrates that "acquired" and "receives" are "interchangeable" with the verb "retain." It demonstrates instead that Congress knew the difference between acquiring title and retaining it. *Sosa v. Alvarez-Machain*, 542 U.S. 692, 711 n.9 (2004) ("[W]hen the legislature uses certain language in one part of the statute and different language in another, the court assumes different mean-

ings were intended.") (internal quotation marks omitted); *see also* 2A Norman J. Singer & J.D. Shambie Singer, *Sutherland Statutes and Statutory Construction* § 46:6 (7th ed. 2009).[5]

Contrary to the government's contentions (*Amicus* Brief of United States 20-22), nothing in Section 210(a) demonstrates that Congress intended "invention of the contractor" to mean "invention of the contractor's employees" or "retain" to mean "acquire." Section 210(a) states that the Bayh-Dole Act "shall take precedence over any other Act which would require a disposition of rights in subject inventions of . . . contractors in a manner that is inconsistent with this chapter." 35 U.S.C. § 210(a). At the threshold, recognizing that rights in inventions vest initially in their inventors would pose no "inconsisten[cy] with this chapter" so long as the definition of "subject invention" remains limited to "inventions of the contractor" (*i.e.*, assigned inventions) as Section 201(e) prescribes, and is not enlarged to include unassigned inventions of the contractor's employees. Moreover, the Patent Act of which "this chapter," the Bayh-Dole Act, is a part, is not "any other Act" over which the Bayh-Dole Act may take precedence. It is the Patent Act that has for 220 years provided that rights in inventions vest initially in the inventor and

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[5] Stanford argues that "retain" must have the same meaning as "acquire" because Section 203 refers to "acquir[ing] title under this chapter" and that the only means of acquiring title found in the "chapter" is Section 202(a)'s election to retain title. "Acquire" can be given its ordinary meaning, however, if rather than "acquired," "under this chapter" modifies "title" to mean "title" subject to the restrictions set forth in the Act. *See* 35 U.S.C. § 202(a).

pass only by valid, written assignment. Nothing in the text of the Bayh-Dole Act even remotely suggests that Congress intended to disturb that fundamental precept of patent law. Instead, the text of the Act reflects a background understanding that federal contractors would acquire rights in inventions made by their employees by assignment language in the employment agreement or otherwise. Senator Bayh himself has acknowledged this understanding. Birch Bayh, Joseph P. Allen & Howard W. Bremer, *Universities, Inventors and Bayh-Dole*, 79 Pat., Trademark & Copyright J. 167, 168 (2009) ("[t]he Bayh-Dole Act is based on the expectation and assurance that such agreements are in place in the university sector").

2. The Department of Commerce's regulations mandating the use of certain language in funding agreements under the Bayh-Dole Act likewise reflect the understanding that the university will secure patent rights by traditional contract with inventors.

The regulations instruct all contractors "to require, by written agreement," their technical employees "to execute all papers necessary . . . to establish the government's rights in the subject inventions." 37 C.F.R. § 401.14(f)(2). The "papers necessary" to "establish the government's rights" consist principally of a written assignment of rights pursuant to 35 U.S.C. § 261. *Dubilier*, 289 U.S. at 187 ("A patent is property and title to it can pass only by assignment."); *see also Solomons*, 137 U.S. at 346 ("nor does the mere fact that an inventor is at the time of his invention in the employ of the government transfer to it any title to, or interest in it").

These regulations demonstrate that the agency charged with administering the Bayh-Dole Act (*see*

35 U.S.C. § 206) understood that inventors would initially possess the rights in their inventions developed with federal funding and that a "written agreement" is necessary to convey rights in the invention to the government. 37 C.F.R. § 401.14(f)(2).

Under Stanford's interpretation of the Act, however, there would be no need for such a regulation requiring an employee "to execute all papers necessary . . . to establish the government's rights" in a federally funded invention. 37 C.F.R. § 401.14(f)(2). So long as the employee timely filed an application for a patent, Stanford and the government would obtain all the rights in the employee's invention by operation of law, regardless of any contract or assignment the employee might have executed in the past. Stanford's and the government's interpretation of the Act thus renders the Department of Commerce's regulation substantially superfluous, which may explain why the Department of Commerce did not sign the Brief of the United States.

3. Nor does the historical background of the Bayh-Dole Act support Stanford's effort to read traditional inventorship and assignment rights out of the Bayh-Dole regime. As Stanford observes, prior to the Bayh-Dole Act, "the Government had no uniform policy to determine the ownership of patents." Pet. Br. 2. Instead, there existed a "melange of 26 different agency policies on vesting of patent rights," H.R. Rep. No. 96-1307, pt. 1, at 3 (1980), *reprinted in* 1980 U.S.C.C.A.N. 6460, 6462. Some of the predecessors to the Bayh-Dole Act *explicitly* required that rights to certain inventions vest in the government. *See, e.g.*, 42 U.S.C. § 2457(a). Other agencies "depended upon the university or nonprofit organization obtaining an assignment of rights from the researcher." *Amicus*

Brief of United States 4 (citing Federal Council for Sci. & Tech., *Report on Government Patent Policy* 330-31, 342 (1976) and 42 U.S.C. § 1871(a) (1976)).

While the Bayh-Dole Act certainly was intended to bring uniformity to this "melange," there is nothing in the statutory history to suggest that the uniformity Congress intended to impose was automatic divestment of inventors and assignees (except, presumably the employing contractor) of all rights in inventions created with the assistance of federal funding. That change would have upended 220 years of practice and at least two of this Court's precedents. *See Dubilier*, 289 U.S. at 187; *Solomons*, 137 U.S. at 346. We assume that, "when Congress enacts statutes, it is aware of relevant judicial precedent," *Merck & Co. v. Reynolds*, 130 S. Ct. 1784, 1795 (2010), and that when it intends a sea change in the law, it will "ma[k]e it explicit in the statute." *Chisom v. Roemer*, 501 U.S. 380, 396 (1991). Here, Congress authorized a contractor only to "elect to retain title" to an "invention of the contractor conceived or first actually reduced to practice . . . under a funding agreement." 35 U.S.C. §§ 201(e), 202(a). That language hardly expresses an intention to divest an inventor of his invention, and "Congress' silence in this regard can be likened to the dog that did not bark." *Chisom*, 501 U.S. at 396 n. 23.

II. Stanford's Interpretation Of The Bayh-Dole Act Threatens The Very Collaboration It Was Intended To Foster.

The Bayh-Dole Act was intended "to promote collaboration between commercial concerns and nonprofit organizations, including universities." 35 U.S.C. § 200. But Stanford's novel interpretation of

the Act will discourage rather than promote collaboration by incentivizing universities and other contractors to engage in predatory behavior to maximize their monetizable intellectual property at the expense of their collaborators. Further, because in Stanford's and the government's view title to subject inventions vest in universities "by operation of law," *Amicus* Brief of United States 13, commercial concerns cannot even use contracts to protect their intellectual property from seizure by an erstwhile collaborator. This, manifestly, is not what Congress intended.

Three plausible scenarios suffice to demonstrate the damage Stanford's and the government's construction of the Act will cause to industrial-academic collaborations.

1. Under Stanford's view, a university may escape its contractual obligations and terminate a commercial collaborator's rights in an invention merely by salting a research project with federal funds. For example, a company with special expertise in one field may collaborate with university researchers with different expertise. Ordinarily, prior to the collaboration, the company and university would have a collaboration agreement in place that specifies how the rights in any resulting patents will be shared. But on Stanford's view, even if the university and the company had agreed that the patents would be jointly owned, the university could vitiate that agreement and seize all of the company's rights in the patents simply by using federal money in reducing the inventions to practice.

Indeed, because an invention may become a "subject invention" *either* at the time it is conceived *or* at the time it is first actually reduced to practice, 35

U.S.C. § 201(e), a university could initiate federal funding to seize the rights in the invention years *after* the invention was conceived—just as long as the first federal dollar is spent before the invention is actually reduced to practice. In fact, because *actual* reduction to practice may not occur until long after the patent has issued (the filing of a patent application demonstrates only *constructive* reduction to practice, *see Weil v. Fritz*, 572 F.2d 856, 865-66 n.16 (C.C.P.A. 1978) (citing *Automatic Weighing Mach. Co. v. Pneumatic Scale Corp.*, 166 F. 288, 297 (1st Cir. 1909))), Stanford's interpretation could allow a university to seize its collaborators' interests in a patent even after the patent has issued.

2. If Stanford's interpretation of the Bayh-Dole Act were correct, a company could be stripped of its rights in an invention even if it had not entered into a collaboration at all. For example, a company employee may conceive of an invention while at the company, file a patent application while at the company, assign all rights in the application to the company, and then leave the company for a faculty position at a university, where she finally reduces the invention to practice.

On Stanford's view, if the university chose to fund its new employee's research with some federal funds, the university owns the previously assigned patent application. The university could have all the rights in that invention—and the company that employed the inventor, paid for the research, and received a then-valid assignment of the patent application would have none. And because the Bayh-Dole Act covers "work funded . . . in part by the Federal Government," 35 U.S.C. § 201(b), use of even a single

federal dollar could divest the company of its rights in the patents.

3. A company similarly may run afoul of Stanford's reading of the Bayh-Dole Act when hiring employees. For example, a university student, with no contract with the university regarding inventions, may conceive of an invention while working in a university lab. Upon graduation, the student may secure employment at a company and present the invention to the company. After the new employee assigns his rights in the invention to the company, the company may invest in the development of the invention and cause the inventor to file a patent application. Under this Court's precedents, the lack of any contract with the university allows the student to own his invention outright and assign the patent rights to the company. *See Solomons*, 137 U.S. at 346. But, in Stanford's view, if the student's laboratory received federal funding, the university or the government may seize title to any resulting patent.

Congress could not have intended the Bayh-Dole Act, enacted to foster collaboration between universities and the commercial sector, to generate such unsettling and disquieting results.

Stanford claims the massive disincentives to collaboration created by its interpretation are justified by its desire for "[a]bsolute assurance" of its title in intellectual property without incurring the cost of "combing through the files of each faculty member" to determine whether they have assigned their inventions to others. Pet. Br. 47. But Stanford bears this burden easily enough with respect to inventions that do not benefit from federal funding.

On the other hand, it makes no sense at all to foist on commercial companies the burden of

monitoring *university* employees to ensure the university does not taint the joint project with federal funding. Collaborating companies have extremely limited abilities to monitor university faculty and other employees; nor can a company effectively monitor the university administration, which decides how and when to spend the federal grants they apply for and receive. Universities are in the best position—far better at least than their commercial partners—to monitor the behavior of their employees. *See generally* Guido Calabresi, *The Costs of Accidents: A Legal and Economic Analysis* 135-38 (1970). While universities may find the exercise of diligence with respect to their employees inconvenient, Stanford's approach would require a commercial company seeking to protect its interest in inventions it developed to exercise powers of clairvoyance—to see not only whether a university had salted a project with federal funds in the past, but also whether they might do so in the future. Lacking such supernatural powers, commercial companies would collaborate with universities or allow employees to work at university labs only at their peril. This would inevitably chill the collaboration the Act was meant to foster. *See* 35 U.S.C. § 200.

CONCLUSION

The judgment of the Court of Appeals for the Federal Circuit should be affirmed.

Respectfully submitted.

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AMICUS CURIAE BRIEF

21

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BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR UNIVERSITY,

Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES
COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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INTEREST OF AMICUS CURIAE

Amicus curiae Intellectual Property Owners Association (IPO) is a trade association representing companies and individuals in all industries and fields of technology who own or are interested in U.S. intellectual property rights.[1] IPO's membership includes more than 200 companies and more than 11,000 individuals who are involved in the association either through their companies or as inventor, author, executive, law firm, or attorney members. Founded in 1972, IPO represents the interests of all owners of intellectual property. IPO regularly represents the interests of its members before Congress and the Patent and Trademark Office and has filed *amicus curiae* briefs in this Court and other courts on significant issues of intellectual property law. The members of IPO's Board of Directors, which approved the filing of this brief, are listed in the Appendix.[2]

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[1] No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than the *amicus curiae* or its counsel made a monetary contribution to its preparation of submission. Both parties in this case consented to the filing of *amicus* briefs in support of either party or neither party by letters submitted to this Court on December 3 and December 6, 2010.

[2] IPO procedures require approval of positions in briefs by a three-fourth majority of directors present and voting. Hoffmann-La Roche, Inc., parent company of Roche Molecular Systems, Inc., is a member of the IPO Board of Directors; however, it did not participate in discussions regarding or vote on the decision to file this brief and did not participate in its preparation.

INTRODUCTION

The Bayh-Dole Act, 35 U.S.C. §§ 200-212 (the "Act"), gives nonprofit institutions and small businesses the option to "retain title" to patents resulting from federally funded research. This case involves an important question of the Act's applicability to an invention that had already been assigned to a third party before any federally funded work had been performed.

The case arises out of a claim by Stanford University against Roche Molecular Systems, Inc. (and associated Respondents) for infringement of a patent covering a method for quantifying the amount of HIV virus in a patient's bloodstream in order to measure the efficacy of antiretroviral drugs. Pet. App. 2a-3a. Roche asserted a defense and counterclaim that it was a co-owner of the patent by virtue of its acquisition of Cetus, a private laboratory where one of the named inventors, Dr. Mark Holodniy, conceived of the technique that ultimately became the basis for the patent. Pet. App. 4a-6a.

As litigated below, the case primarily involved the question of which assignment agreement executed by Dr. Holodniy took priority: (a) an agreement with Stanford, the university that employed him, "to assign or confirm in writing to Stanford and/or sponsors that right, title and interest in . . . such inventions as required by Contracts or Grants," or (b) a later agreement Dr. Holodniy made with Cetus — the private laboratory where he developed the basic technology that led to the invention — in which Dr. Holodniy agreed that he "will assign and do[es] hereby assign to CETUS, my right, title and interest in each of the ideas, inventions and improvements" that Dr. Holodniy

may devise "as a consequence of" his work at Cetus. Pet. App. 12a-15a (internal quotation marks omitted). The Federal Circuit held that the agreement with Cetus, of which "Stanford had at least constructive or inquiry notice," Pet. App. 16a, effected an immediate assignment of any invention arising out of Dr. Holodniy's work at Cetus and thus took precedence over his prior agreement with Stanford, and that, since Roche is the co-owner of the patent, Stanford lacks standing to sue. Pet. App. 14a, 28a.

As one of its secondary arguments below, Stanford also claimed that, even if Dr. Holodniy's assignment to Cetus were otherwise valid, Stanford's receipt of federal funding for the clinical testing that confirmed the utility of the methodology developed by Dr. Holodniy at Cetus entitled Stanford to elect to become the owner of the invention and the resulting patents, under section 202(a) of the Bayh-Dole Act. That provision grants to nonprofit organizations and small business firms the right to "retain title" to "subject inventions," except in certain specified circumstances where such rights would be transferred to the federal government. 35 U.S.C. § 202(a); *see also* Pet. App. 18a. In making this argument, Stanford maintained that the statute gives it full and exclusive title to the invention even if Cetus acquired the rights of Dr. Holodniy's contribution to the invention prior to Stanford's receipt of funding under the Bayh-Dole Act. Pet. App. 18a-19a.[3]

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[3] There is no dispute that Stanford is at least a co-owner of the patent by virtue of its government funded clinical research activities by other named inventors who were not subject to any agreement with Cetus. Pet. App. 3a-4a.

The U.S. Court of Appeals for the Federal Circuit summarily rejected Stanford's argument, holding that "Stanford identifies no authorities or reasons why its election of title under Bayh-Dole had the power to void any prior, otherwise valid assignments of patent rights." Pet. App. 19a. Nevertheless, Stanford's merits brief in this Court, and a supporting *amicus curiae* brief filed by the United States, take the position that, whatever rights Cetus may have acquired by virtue of its agreement with Dr. Holodniy, those rights were lost when Stanford used government funding for the clinical testing that ultimately resulted in the issuance of the patent. Pet. Br. 26, 32; U.S. Br. 17-19.

For purposes of this *amicus* brief, IPO takes no position on the merits of the Federal Circuit's holding that Cetus had acquired ownership of the patent rights prior to the commencement of the federally funded research, but assumes, *arguendo,* that the Federal Circuit's resolution of that question, and all of the remaining issues involved in this case other than the potential impact of Bayh-Dole, were correct.[4] Rather, this brief focuses on the issue of

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[4] In its merits brief before this Court, Stanford argues for the first time that Dr. Holodniy's work at Cetus (and consequent conception of the patented invention at issue) was supported by federal research funding that was in place prior to Dr. Holodniy's work at Cetus. *See* Pet. Br. 17, 32-33 & n.12. However, it is unclear whether there was an agreement with Bayh-Dole provisions executed in connection with such funding and, in any event, the Federal Circuit's decision was premised on the assumption (apparently unchallenged during that appeal) that the work at Cetus was performed prior to the receipt of federal funding. The District Court found that (1) "the invention was *clearly conceived* at the latest when Holodniy had developed the PCR assay"; (2) "[t]he specific method of using the assay to monitor HIV treatment was . . . clear in the minds of Holodniy and the other Stanford scientists when the assay was completed at Cetus"; and (3) "the invention was

IPO's primary concern — the proper construction of the Bayh-Dole Act and the impact of the Act on the rights of third parties acquired from the inventor before any federally funded work was performed.

SUMMARY OF ARGUMENT

The express language and the legislative purpose of the Bayh-Dole Act require that, in order for an invention to qualify as a "subject invention" under its provisions, *see* 35 U.S.C. § 201(e), the rights to the invention must not only be conceived or actually reduced to practice in the course of work performed under a funding agreement, but must also be owned by the contracting party at the time that governmentally funded work is performed. Thus, section 202(a) of the Bayh-Dole Act does not permit a contractor receiving federal funding to acquire rights to an invention which, as the Federal Circuit found in this case, had previously been assigned to another party.

Allowing Stanford, by virtue of obtaining federal funding, to eliminate rights acquired by a third party for fair consideration, and to subsequently sue that party for infringement, would be contrary to the intent of the Bayh-Dole Act to encourage private development of governmentally-funded research and to promote cooperation between nonprofit and private research institutions. Instead, Stanford's

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conceived during Holodniy's consultancy at Cetus . . . ," Pet. App. 56a-58a, and those findings were not challenged in the Federal Circuit. In addition to its holding on the relative effectiveness of the two assignment agreements, the Federal Circuit reversed the district court's finding that Roche's defense based on co-ownership of the patent was barred by the statute of limitations. Pet. App. 22a-27a.

proposed construction of the Bayh-Dole Act would discourage collaboration between academic institutions and private companies by creating a potential cloud on a private entity's lawfully acquired patent rights.

Indeed, any construction of the Bayh-Dole Act that would transfer the rights of the owner of a patented invention to another party without obtaining the consent of or paying compensation to the owner of those rights should be avoided as potentially raising a serious constitutional issue under the Takings Clause of the Fifth Amendment to the United States Constitution.

ARGUMENT

A. The Express Language of the Bayh-Dole Act Limits Its Applicability to Patent Rights Owned or Controlled by the Federal Contractor.

The "starting point in every case involving construction of a statute is the language itself." *Landreth Timber Co. v. Landreth*, 471 U.S. 681, 685 (1985) (internal quotation marks and citations omitted). In this case, the language of the Bayh-Dole Act, as reflected in the definitional provisions of section 201 and the operative provisions of section 202, mandates the conclusion that an invention does not become subject to the provisions of the Bayh-Dole Act unless it is owned by the party that contracts for the government funding at the time that the invention is either conceived or actually reduced to practice.

In order to fall within the scope of the Bayh-Dole Act, a patented invention must constitute a "subject

invention." Section 201 of the Act defines that term as follows:

> The term "subject invention" means any invention *of the contractor* conceived or first actually reduced to practice in the performance of work under a funding agreement . . . .

35 U.S.C. § 201(e) (emphasis added).

By its plain terms, this provision sets forth a two-prong test for an invention to qualify as a "subject invention" under the Act: first, the invention must be "an invention of the contractor"; and, second, the invention must have either been "conceived or first actually reduced to practice in the performance under a funding agreement" with the federal government.

Without citing any authority or providing any reasoning, Stanford deals with this language by simply assuming that, since only natural persons can be inventors, the term "'invention of the contractor'" must mean "all inventions made by *the contractor's employees* with the aid of federal funding." Pet. Br. 32 (quoting 35 U.S.C. § 201(e)) (emphasis added); *see also id.* at 33 ("[The invention claimed by the patents-in-suit] was an 'invention of the contractor' because the named inventors on the patents-in-suit . . . were researchers employed by Stanford."). However, nothing in the Act or its legislative history remotely suggests (as even Stanford tacitly concedes, *see* Pet. Br. at 32 n.10) that Congress intended the determination of whether an invention is an "invention of the contractor" to turn solely on the employment status of the individual inventors.[5]

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[5] The United States' brief deals with the definition of "subject

Since, in fact, the contractor can never actually be the inventor, and the statute clearly differentiates between inventors and contractors (*see, e.g.*, 35 U.S.C. § 202(d), (e)), a more reasonable construction of the term "invention of the contractor" is that the invention must *belong to* the contractor; *i.e.*, that the contractor must have acquired the rights from the inventor. This construction, unlike Stanford's, is not only consistent with the plain language of the Bayh-Dole Act, but also with this Court's precedents interpreting similar language in other statutory provisions. *See, e.g.*, *Ellis v. United States*, 206 U.S. 246, 259 (1907) (construing the phrase "the public works of the United States" as meaning works "*belonging to* the United States") (internal quotation marks omitted) (emphasis added); *see also Flores-Figueroa v. United States*, 129 S. Ct. 1886, 1888-89 (2009) (treating "knowingly" possessing "*a* means of identification *of* another person" as meaning that "the defendant knew that the 'means of identification' . . . *belonged to* 'another person'") (internal quotation marks omitted) (emphasis altered).

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invention" by simply ignoring the portion of the definition that limits its applicability to an "invention of the contractor." *See* U.S. Br. 5, 17. By ignoring the words "of the contractor," the United States violates "a cardinal principle of statutory construction," rendering those words entirely "superfluous, void, or insignificant." *TRW Inc. v. Andrews*, 534 U.S. 19, 31 (2001) (internal quotation marks and citations omitted). In order to "give effect . . . to every clause and word of a statute," *United States v. Menasche*, 348 U.S. 528, 538-539 (1955) (internal quotation marks and citation omitted), this Court should recognize that 201(e)'s definition of a "subject invention" as "an invention *of the contractor*" imposes an additional requirement that must be met in order for an invention to be deemed a "subject invention" under the Bayh-Dole Act.

The language of section 202(c) of the Bayh-Dole Act provides further confirmation that the Act was not intended to confer greater rights on the federal contractor than the contractor already owned. That section provides, in several instances, that the only right that the contracting nonprofit institutions and small businesses are granted under the statute and a funding agreement made pursuant thereto is the right to "retain title" — that is, to keep title to the extent that the contractor already had such title. *See* Webster's Third New International Dictionary 1938 defn. 2a (1976) (defining "retain" as "to hold or continue to hold in possession or use"); Black's Law Dictionary 1183 (5th ed. 1979) (defining "retain" as "[t]o continue to hold, have, use, recognize, etc., and to keep").

Specifically, section 202(a) reads as follows:

> Each nonprofit organization or small business firm may, within a reasonable time after disclosure as required by paragraph (c)(1) of this section, elect to *retain title* to any subject invention . . . .

35 U.S.C. § 202(a) (emphasis added).

Similarly, section 202(c) mandates:

> Each funding agreement with a small business firm or nonprofit organization shall contain appropriate provisions to effectuate the following:
>
> * * *
>
> (2) That the contractor make a written election within two years after disclosure to the Federal agency (or such additional time as may be approved by the Federal agency)

> whether the contractor will *retain title* to a subject invention . . . .

35 U.S.C. § 202(c) (emphasis added).

Notably, when the statute speaks of transferring title to the government, it uses different language. Thus, section 202(c) provides that "the Federal Government may *receive* title to any subject invention in which the contractor does not elect to *retain* rights or fails to elect rights within [statutorily prescribed] times." 35 U.S.C. § 202(c)(2) (emphasis added). "'[W]hen the legislature uses certain language in one part of the statute and different language in another, the court assumes different meanings were intended.'" *Sosa v. Alvarez-Machain*, 542 U.S. 692, 711 n.9 (2004) (quoting 2A Norman J. Singer, Statutes and Statutory Construction § 46:06, at 194 (6th rev. ed. 2000)).[6]

This statutory construction is further supported by the structure of section 202(c), which requires that the terms under which the contractor may "retain" and the government may "receive" title to inventions under the Act be embodied in a contract between the contractor and the government. 35 U.S.C. § 202(c) ("Each funding agreement with a small business firm or nonprofit organization shall contain appropriate provisions to effectuate the following [requirements of the statute] . . . ."); *see also* 37 C.F.R. §§ 401.3(a), 401.14(a) (requiring the

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[6] It is also worth noting that the original House version of the bill that ultimately became the Bayh-Dole Act stated that the contractor could "acquire title" under certain circumstances. *See* H.R. 6933, 96th Cong. § 383(a) (as passed by House, Nov. 17, 1980). The Senate replaced that language with the words "retain title" that appear in the statute as it was ultimately enacted. *See* H.R. 6933, 96th Cong. § 202(a) (as passed by Senate, Nov. 20, 1980).

inclusion of a standard patent rights clause in all federal funding agreements). The fact that Congress required the Act's provisions to be embodied in a contract further evidences its intent to limit its provisions to parties who expressly consent to the provisions of the Act, and not to eliminate or alter the lawfully acquired rights of third parties who have not consented to its provisions or entered into an agreement with the United States.[7]

B. The Statutory Construction of the Bayh-Dole Act Advanced by Stanford and Its *Amici* Would Frustrate the Objectives of the Act and Discourage Academic-Industry Collaboration.

The proposed construction of the Bayh-Dole Act advanced by Stanford and its *amici* would lead to results that are contrary to the Bayh-Dole Act's stated objectives of "promot[ing] the utilization of inventions arising from federally supported research and development" and "promot[ing] collaboration between commercial concerns and nonprofit

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[7] Stanford and the United States, as *amicus curiae*, seek support in the Bayh-Dole Act's use of the terms "acquire[]" and "receive[]" in other provisions of the Act when describing the contractor's rights under the statute. *See* Pet. Br. 36 (quoting 35 U.S.C. §§ 203(a), 204); U.S. Br. 21 (same). Sections 203(a) and 204, however, address entirely different aspects of the statutory regime from the question of what patent rights are granted to contractors under the Bayh-Dole Act. Thus, section 203 concerns the government's march-in rights, 35 U.S.C. § 203, and section 204 sets forth a preference for domestic U.S. manufacturing, 35 U.S.C. § 204. The provisions that actually determine the rights acquired by the United States and contracting parties are set forth in section 202 of the Act and the mandatory language of the funding agreement made pursuant to that section.

organizations, including universities." 35 U.S.C. § 200. Permitting a university, by obtaining government funding, to deprive a private research organization of patent rights that it had previously contracted for in good faith and for good and valuable consideration would discourage private companies from working with university personnel out of fear of loss of their rights and, indeed, possible liability for patent infringement based on inventions developed using their facilities and proprietary information.

The Bayh-Dole Act was drafted and enacted between 1979 and 1980, during a period of relative economic and industrial decline in the United States and corresponding rise of foreign industrial powers. The enactment of the Bayh-Dole Act was largely driven by the desire to lift the country out of this slump by spurring the licensing to industry of patented inventions arising from federally-funded research projects. *See, e.g.*, 126 Cong. Rec. 30364 (1980) (statement of Sen. Bayh); *id.* at 30366 (statement of Sen. Dole).

Prior to the Bayh-Dole Act, patents for inventions that were invented within universities under at least partial federal funding were frequently claimed by the federal government and licensed nonexclusively to all comers. *See* S. Rep. No. 96-480, at 2 (1979). Most private companies had no interest in commercially developing such inventions without an exclusive license since they would otherwise gain no competitive advantage from their investment. *See, e.g., The University and Small Business Patent Procedures Act, Part 1: Hearings Before the S. Comm. on the Judiciary*, 96th Cong. 2 (1979) (statement of Sen. Bayh, Member, S. Comm. on the Judiciary) ("[T]he agencies have had very little success in attracting private industry to develop and market these inventions because when the agencies

retain the patent rights there is little incentive for any company to undertake the risk and expense of trying to develop a new product."); S. Rep. No. 96-480, at 2 (noting that "of the more than 28,000 patents in the Government patent portfolio, less than 4 percent are successfully licensed").

The Bayh-Dole Act sought to remedy this by creating a uniform path toward the exclusive licensing of federally-funded inventions to private industry. For inventions already owned by the federal government, the Bayh-Dole Act enabled federal agencies to grant exclusive licenses and partially exclusive licenses to private industry. *See* 35 U.S.C. §§ 207(a)(2), 209. For inventions developed with federal funds by nonprofit organizations (e.g., universities) or small businesses, the Bayh-Dole Act generally granted these contractors an option to retain title to the patents so that they could then license exclusively to private industry for commercialization. *See, e.g.*, S. Rep. No. 96-480, at 2 (noting that while only 4 percent of the federal patent portfolio had been licensed, "[u]niversities . . . which can offer exclusive or partially exclusive licenses on their patents if necessary, have been able to successfully license 33 percent of their patent portfolios"); *see also* 126 Cong. Rec. 1798 (1980) (statement of Sen. Thurmond).

The sponsors of the Bayh-Dole Act were particularly concerned that patented inventions in the biomedical field were left unlicensed and undeveloped, when they could be saving lives in the hands of a financially-incentivized company. *See* 126 Cong. Rec. 30366 (1980) (statement of Sen. Dole) ("In the field of medical innovation, the obstruction of patent rights by Federal agencies is an extremely serious problem. Indeed, when medical inventions offering potential cures for diseases are withheld, it

is the very lives of Americans which are affected."); *id.* at 8740 (statement of Sen. Bayh) (providing a list of "over 30 promising medical discoveries" that were not developed due to government delays in deciding ownership of patent rights); S. Rep. No. 96-480, at 21 (attributing the failure to develop drugs from federally-funded research to the "lack of incentives to the private sector to commit the time and money needed to commercialize these discoveries").

The construction of the Bayh-Dole Act urged by Stanford and the United States, however, would turn this purpose on its head. Instead of encouraging universities to grant exclusive rights to private industry, it would permit a university, simply by obtaining a federal grant, to acquire exclusive rights that had previously been granted to a private company for valuable consideration under a valid agreement. Further, the university could then turn around and sue the very company that had provided the facilities and information that led to the invention, simply because the university subsequently conducted further research under a federal grant which the private company neither sought nor consented to.

Stanford's reading of the Bayh-Dole Act would deprive private companies of certainty in their patent rights, thereby chilling academic-industry collaboration. Consider the example of a university employee (not funded by any federal grants covered by the Bayh-Dole Act) who, with the university's consent, accepts a compensated research position at a private company alongside his university post. The researcher benefits from the company's facilities and resources, and the company may expend considerable funds on his work. To protect its investment, the private company ordinarily would require the researcher to assign to it any inventions that arise

from his work at the company. Stanford's construction of the Bayh-Dole Act, however, would permit the university to subsequently reduce to practice any invention resulting from the researcher's work at the company (which did not benefit from any federal grants) using Bayh-Dole funds and divest the private company of its patent rights entirely.

By exposing private organizations to the possibility of forfeiture of their rights — and even to legal liability — the construction of the statute urged by Stanford and the United States would defeat the express goals of the statute. In so doing, it would also *sub silentio* create a broad exception to the longstanding and well established principle of patent law that an individual inventor, and no one else, owns the rights to his inventions in the first instance and has the initial right to assign those rights, including the patent rights arising therefrom. *See* 35 U.S.C. § 261; 8 Donald S. Chisum, *Chisum on Patents* § 22.01, at 22-2 (1993); *United States v. Dubilier Condenser Corp.*, 289 U.S. 178, 187 (1933).[8]

Indeed, the United States as *amicus curiae* expressly advances the argument that the Bayh-Dole Act "take[s] precedence" over the fundamental statutory and common law principle that "the right

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[8] It has long been settled that title to a patented invention vests in the first instance to the inventors. *See, e.g., Crown Die & Tool Co. v. Nye Tool & Mach. Works*, 261 U.S. 24, 35-36 (1923); *Manual of Patent Examining Procedure* § 301 (8th ed. 2010) ("The ownership of the patent . . . initially vests in the named inventors of the invention of the patent.") (citing *Beech Aircraft Corp. v. EDO Corp.*, 990 F.2d 1237, 1248 (Fed. Cir. 1993)). The inventor's ownership right in a patent is treated as an interest in personal property, and it follows that the inventor may assign that interest to another person or entity. *See* 35 U.S.C. § 261; *Crown Die & Tool Co.*, 261 U.S. at 36-37.

to obtain a patent on an invention . . . belongs to the inventor, who may assign that right." *See* U.S. Br. at 21 & n.2 (citing 35 U.S.C. §§ 101, 115, 116, 152) (internal quotation marks omitted). As this Court has explained, as a general matter, in the field of patent law "congressional action should not be overread for negative implications." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 28 (1997); *see also Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002) (stating that "[t]he responsibility for changing [settled patent law] rests with Congress" and that "[f]undamental alterations in these rules risk destroying the legitimate expectations of inventors in their property"). Yet, there is absolutely nothing in the language of the Bayh-Dole Act, its legislative history, or any of the contemporaneous discussion of the proposed legislation or its intended effect that even hints at any intent to overturn the well-established rule that an employer must obtain an assignment agreement from its employees if it wishes to obtain ownership of their inventions.[9]

Stanford and *amici* argue extensively that if universities were required to obtain proper assignments from their employees in order to retain

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[9] The United States' reliance on 35 U.S.C. § 210(a), *see* U.S. Br. at 21, is misplaced. That provision was only intended to assure that the Act takes precedence over prior laws that were "inconsistent" with the Act, citing twenty-one statutes that governed the disposition of federally-funded inventions prior to its enactment. It implies nothing whatsoever about the question before this Court — whether the Act was intended to change the fundamental rules governing the ownership of inventions by employees of nonprofit institutions. Section 210(a) merely serves to assure that rules established by the Bayh-Dole Act are applied uniformly and supersede any prior inconsistent rules, but the terms of those rules themselves are set forth in section 202.

title under the Bayh-Dole Act, subsequent licensing activities would "wreak havoc" by requiring an impracticable level of due diligence to discover assignments of which the university may have no notice. *See, e.g.*, Pet. Br. 50-51; U.S. Br. 30-31; NVCA Br. 13-14. However, in the commercial world, private companies that engage in research routinely obtain assignment agreements from their employees, and prospective licensees routinely take measures to ensure that the licensor has clean title to the invention. *See, e.g.*, Mark S. Holmes, *Patent Licensing: Strategy, Negotiations, and Forms* § 11:3.5, at 11-6 (Practicing L. Inst. 2010) ("Licensees should not be shy about seeking assurances that the licensor holds *all* rights necessary to license the covered patents and technology.").[10] As noted above, Bayh-Dole was intended to extend these types of normal commercial licensing practices to government funded research projects, not create a radically different set of rules.

Certainly, nothing in the facts of this case justifies the imposition of fundamentally different principles of patent ownership for employees of nonprofits who obtain government funding. On the contrary, it is clear from the Federal Circuit opinion that, if Stanford had used slightly different language in its agreement with Dr. Holodniy, or if it did not have at least constructive notice of Dr. Holodniy's subsequent assignment agreement with Cetus, it could easily have acquired, and been able to retain,

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[10] Indeed, the federal government itself requires such assurances. The agency-wide implementing regulations for the Bayh-Dole Act provide that "[t]he contractor agrees to require, by written agreement, its employees . . . to execute all papers necessary to file patent applications on subject inventions and to establish the government's rights in the subject inventions." 37 C.F.R. § 401.14(f)(2).

sole title to the invention at issue in this case without requiring any drastic change in the established principles of patent ownership.

In sum, the construction of the Bayh-Dole Act advanced by Stanford and its *amici* would discourage private investment in patentable inventions by allowing nonprofits to retroactively invalidate an otherwise valid agreement by an inventor to convey patent rights to a private party. Such a result would discourage collaboration between commercial developers and persons affiliated with academic research institutions — exactly the opposite of the effect that Congress intended the Bayh-Dole Act to achieve.

C. The Construction of the Bayh-Dole Act Proposed by Stanford and the United States Should Be Rejected Because It May Raise Serious Constitutional Issues Under the Takings Clause of the Fifth Amendment.

As this Court has repeatedly stated, "'where a statute is susceptible of two constructions, by one of which grave and doubtful constitutional questions arise and by the other of which such questions are avoided, [the Court's] duty is to adopt the latter.'" *Jones v. United States*, 526 U.S. 227, 239 (1999) (quoting *United States ex rel. Att'y Gen. v. Del. & Hudson Co.*, 213 U.S. 366, 408 (1909)). "The avoidance canon rests upon [the courts'] 'respect for Congress, which [the courts] assume legislates in the light of constitutional limitations.'" *Harris v. United States*, 536 U.S. 545, 556 (2002) (quoting *Rust v. Sullivan*, 500 U.S. 173, 191 (1991)).

Here, the construction of the Bayh-Dole Act urged by Stanford and the United States would raise a serious constitutional question as to whether a statute mandating the uncompensated, compulsory transfer of title in a patentable invention from a private company to a university or to the government amounts to a violation of the Takings Clause.

This Court's decisions establish that patent rights are a form of property protected by the Takings Clause. *See, e.g.*, 35 U.S.C. § 261 (2006) ("[P]atents shall have the attributes of personal property."); *Festo*, 535 U.S. at 730; *Florida Prepaid Postsecondary Educ. Expense Bd. v. College Sav. Bank*, 527 U.S. 627, 642 (1999); *United States v. Burns*, 79 U.S. (12 Wall.) 246, 252 (1870) ("[T]he government cannot, after the patent is issued, make use of the improvement any more than a private individual, without license of the inventor or making compensation to him."); *Cammeyer v. Newton*, 94 U.S. 225, 234 (1876) (declaring, in a case of patent infringement by federal officials, that "private property, the Constitution provides, shall not be taken for public use without just compensation."); *see also McKeever's Case*, 14 Ct. Cl. 396, 421 (1878) (holding that patents are constitutional private property under the Takings Clause). A patent "confers upon the patentee an exclusive property in the patented invention which cannot be appropriated or used by the government itself, without just compensation, any more than it can appropriate or use without compensation land which has been patented to a private purchaser." *James v. Campbell*, 104 U.S. 356, 358 (1881). Indeed, this Court has expressly held, in an analogous context, that the investment-backed expectations in trade secrets are protected by the Takings Clause of the

Fifth Amendment. *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1001-04 (1984).[11]

The Takings Clause may be implicated not only when the government takes property for its own use, but also when it mandates its transfer to a private entity. *See Kelo v. City of New London*, 545 U.S. 469, 475-77 (2005). Thus, if the Bayh-Dole Act were construed as transferring to a private nonprofit institution, without compensation, the rights to an invention that had previously been assigned to another, such a construction could raise "grave and doubtful constitutional questions," and should be avoided. *Jones*, 526 U.S. at 239 (internal quotation marks and citation omitted).

This Court need not decide whether such a construction of the Bayh-Dole Act would indeed amount to a violation of the Takings Clause. "[W]here an otherwise acceptable construction of a statute would raise serious constitutional problems, the Court will construe the statute to avoid such problems unless such construction is plainly contrary to the intent of Congress." *Edward J. DeBartolo Corp. v. Fla. Gulf Coast Bldg. & Constr. Trades Council*, 485 U.S. 568, 575 (1988) (citing *NLRB v. Catholic Bishop of Chicago*, 440 U.S. 490, 499-501, 504 (1979)). Here, the construction of the Bayh-Dole

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[11] Indeed, during Congressional consideration of the Bayh-Dole Act, the Society of University Patent Administrators, which supports Stanford here, submitted a statement to the Senate Judiciary Committee that "the fifth amendment provides generic protection for all individual property," and that "there is little doubt that the term 'property' as used in the fifth amendment includes intellectual property." *See The University and Small Business Patent Procedures Act, Part 1: Hearings Before the S. Comm. on the Judiciary*, 96th Cong. 194 (June 6, 1979) (written testimony of Howard Bremer, President, Society of University Patent Administrators).

Act that more faithfully reflects both the language of the Act and Congressional intent is one that would obviate the need for this Court to address a potential constitutional issue, and IPO urges this Court to adopt that construction and to hold that the grant of federal funding to a nonprofit institution does not alter pre-existing rights granted by the inventor to a third party.

CONCLUSION

For the foregoing reasons, IPO respectfully requests that the Court hold that the Bayh-Dole Act does not operate to transfer to a nonprofit institution rights to an invention that belonged to another party at the time the invention became subject to the Act's provisions.

Respectfully submitted,

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APPENDIX

APPENDIX[1]

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AMICUS CURIAE BRIEF

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No. 09-1159

IN THE

Supreme Court of the United States

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,
Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC. ET AL.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF THE NATIONAL VENTURE CAPITAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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BRIEF OF THE NATIONAL VENTURE CAPITAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

Amicus curiae respectfully submits this brief in support of petitioner, with the written consent of the parties.[1]

INTEREST OF *AMICUS CURIAE*

The National Venture Capital Association (NVCA), comprised of more than 400 member firms, is the premier trade association for the U.S. venture capital industry. Its members invest in emerging growth companies that strive to bring cutting edge technologies to the market. NVCA's members make venture investments across all industry sectors and at various points in companies' life cycles. As a result, NVCA and its members have witnessed firsthand the importance of the Bayh-Dole Act's straightforward and predictable ownership rules across a broad range of companies and issues. NVCA's members include leading venture capital firms and venture capitalists supportive of this brief, including: William K. Bowes, Jr.; Domain Associates; William H. Draper; Institutional Venture Partners; Interwest Partners; Franklin P. Johnson; Kleiner Perkins Caufield and Byers; Menlo Ventures; Mohr Davidow

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[1] Letters of consent have been filed with the Clerk. No party or counsel for a party to this case authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity other than members of or counsel for *amicus curiae* has made a monetary contribution to the preparation or submission of this brief.

Ventures; Scale Venture Partners; Sequoia Capital; Sigma Partners; and Sutter Hill Ventures.

The venture capital industry, represented by the NVCA, is and has been for many years a principal driver of innovation and growth in the United States economy. It has spawned new industries and led to pioneering and life-changing innovation in biotechnology, health care, software, semiconductors, telecommunications, computer science and communications systems and devices—innovations which have enabled this nation to be the world's economic leader. The names of many successful venture-backed companies are well known: Microsoft and Apple, Genentech and Amgen, Gilead, Google, and Yahoo!, Network Appliances and nVidia, Oracle and Peoplesoft, Cisco and Adobe, eBay and Amazon.

The venture capital industry, and the entrepreneurs and inventors they back, keep the United States at the cutting edge of economic change. It is that group which translates advances in science and technology at our universities into jobs and improved services and health care for people worldwide. Many of those entities were started with university licenses of technology and inventions.

The venture capital industry has a significant interest in this case because the Federal Circuit's decision, if allowed to stand, would tend to discourage private investment in the development and commercialization of federally funded research ideas, and to frustrate the business community's collaborative efforts with nonprofit and university recipients of federal funding.

INTRODUCTION AND SUMMARY

Amicus submits this brief to bring to the Court's attention two significant practical concerns raised by the Federal Circuit's decision below. Both concerns grow out of the extensive experience of *amicus*'s members with the process of developing federally funded research ideas into commercially valuable products and services.

First, the Federal Circuit's decision would tend to discourage venture capitalists and established companies from committing the "risk capital necessary to develop [federally funded] inventions to the point of commercial application." H.R. Rep. No. 96-1307, pt. 1, at 3 (1980), *reprinted in* 1980 U.S.C.C.A.N. 6460, 6462. The Bayh-Dole Act has facilitated such investment because it has long been understood to create a clear and predictable ownership framework. The decision below undermines that framework, however, leaving in its place a regime under which venture capital firms cannot easily determine who holds the rights to a federally funded research idea. This uncertainty would discourage the commitment of the risk capital needed to develop and commercialize raw research ideas.

Second, the decision below would tend to stifle cooperative efforts between the business community and university faculty. If, as the Federal Circuit held, individual researchers (faculty, post-doctoral students, or other graduate students) may assign away the rights to future inventions, universities might restrict and police the activities of those researchers in order to protect the ownership of the patents, instead of encouraging technology transfer

through faculty-industry interaction contemplated by the Act. Moreover, the decision could discourage successful former startups and established companies from funding research and development in academia through sponsored research agreements. Companies' participation in these cooperative ventures is contingent on the integrity and clarity of their licensing and assignment arrangements with universities.

ARGUMENT

A. The Federal Circuit's Decision Would Discourage Private Investment In The Development And Commercialization Of Federally Funded Research Ideas

In enacting the Bayh-Dole Act, Congress sought to encourage the commitment of risk capital to the development and commercialization of inventions arising out of federally funded research. Over the past three decades, *amicus*'s members have helped to make Congress's vision a reality. This has been possible because the Act was long understood to establish a straightforward and predictable ownership framework. Under that framework, the universities and other nonprofits conducting federally sponsored research may, on behalf of themselves and the researchers, negotiate licenses with venture-backed companies willing to invest in those inventions as needed for commercialization.

The Federal Circuit's construction of the Act, however, clouds the ownership of federally funded inventions, and thus clouds the enforceability of the licenses. The Federal Circuit's approach allows the side agreements of individual co-inventors to trump

the statutory ownership rights of universities and other nonprofit research institutions. The resulting uncertainty would discourage venture capital firms and established companies from investing in the process of bringing government funded research to the market.

1. a. A central purpose of the Bayh-Dole Act was to "encourage . . . the commitment of the risk capital necessary to develop [federally funded] inventions to the point of commercial application." H.R. Rep. No. 96-1307, pt. 1, at 3, *reprinted in* 1980 U.S.C.C.A.N. at 6462. Private investment is essential because invention "is in many ways the easy bit"; by a recent estimate, a "dollar's worth of academic invention or discovery requires upwards of $10,000 of private capital to bring to market," meaning that "companies that license ideas from universities wind up paying over 99% of the innovation's final cost." Opinion, *Innovation's Golden Goose*, The Economist, Dec. 12, 2002, at 3. In the experience of *amicus*'s members, development and commercialization of raw research ideas can cost hundreds of millions of dollars or more.

Venture capital firms play a critical role in committing that essential private capital to promising companies devoted to developing and commercializing inventions arising out of federally funded research.[2] These startup companies obtain licenses

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[2] "Venture capital," sometimes referred to as "risk capital," is an "important source of financing for start-up companies or others embarking on new or turnaround ventures that entail some investment risk but offer the potential for above average future profits." *Barron's Fi-*

(normally exclusive, except where fundamental advances are made, which can attract risk capital even with nonexclusive licenses) from universities and nonprofit research institutions, and they are able to attract venture investment as a result. These efforts lead to the formation of new companies and high paying jobs. Established companies also acquire exclusive licenses from universities and other nonprofit research institutions, and then use their own resources and in-house capacity to develop the federally funded inventions and bring them to market.

This substantial commitment of private capital has been possible because of the Bayh-Dole Act's clear and predictable ownership framework. That framework, as Senator Birch Bayh has explained, "was straightforward and easy to understand. Universities and other nonprofit research institutions would retain ownership of the ideas they developed through government funded research. They could license such patented ideas to industry at large for commercialization and would receive royalties." Senator Birch Bayh, Speech at the Licensing Executives Society 2006 Annual Meeting, *Bayh-Dole: Don't Turn Back The Clock* (Sept. 12, 2006), *reprinted in* les Nouvelles, at 216 (Dec. 2006), *available at* http://mirror.lesi.org/BirchBayh/Bayh.pdf. In light of this predictable rule, a startup company holding an exclusive license from a university, for example, could easily prove that the ownership of its license was valid simply by pointing to its agreements with the university. No further inquiry or investigation

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nance & Investment Handbook 945 (7th ed., John Downes & Jordan Elliot Goodman eds., 7th ed. 2007).

was required. As a result, venture capital firms have been able to invest in startups with sound business plans, without worrying about whether those plans are premised on licenses of technology of questionable ownership. Likewise, licensees could devote substantial time and resources to developing and commercializing federally funded research, without worrying about whether the nonprofit that granted them an exclusive license actually owned the invention it purported to license.

This licensing certainty is highly significant to *amicus*'s members. Venture capital firms (and established companies) that invest in the commercialization of federally funded research ideas *already* take on a significant amount of investment risk. As an initial matter, they assume the risk that their resources could have been better invested elsewhere. At the back end, they face the risk that the product they have helped bring to market will not fare well in that market or might not work as hoped, or that the underlying invention will turn out not to have been patentable. Different products also entail various types of regulatory risk. For instance, investments in pharmaceutical innovation face the risk that the new products ultimately will not survive the Food and Drug Administration's extensive approval process. And venture capital firms always face the risk that a startup company will not succeed for any number of reasons. If venture capitalists must also fear that the licenses on which business plans and funding judgments are made will turn out to be unenforceable because of questions about ownership, they will be much more likely to conclude that the other risks are not worth taking.

The Congress that passed the Bayh-Dole Act was well aware of the importance of the Act's simple and predictable ownership rules in encouraging private investment. Congress recognized that the key to "encourag[ing] private industry to utilize government funded inventions through the commitment of . . . risk capital" was to replace the then-existing "melange of 26 different agency policies on vesting of patent rights in government funded research [with] a single, uniform national policy." H.R. Rep. No. 96-1307, pt. 1, at 3, *reprinted in* 1980 U.S.C.C.A.N. at 6462; *see also id.* at 2, *reprinted in* 1980 U.S.C.C.A.N. at 6461.

b. An important feature of the Act's uniform ownership framework has been its placement of a right to elect ownership in the hands of universities and other nonprofits who receive federal funds, rather than in the hands of individual inventors. The nonprofits can grant reliable exclusive licenses in a manner that multiple individual inventors (who may not remember all of the contracts they have signed over the years, and may not have been as careful about signing them) simply cannot. *See infra* A.2.a. In particular, universities—which perform most of the nation's basic research and which cover most of their research expenditures using federal funds[3]—have proved highly capable of allocating exclusive licenses to promising companies.

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[3] *See* Association of American Universities, *University Research: The Role of Government Funding* 1 (May 2006), *available at* http://www.aau.edu/WorkArea/DownloadAsset.aspx?id=1122 (in 2007, universities performed 54% of U.S. basic research); Association of Uni-

It was evident by 1980 that universities had been successful in licensing their portfolios of patents arising out of private funding to startups and other companies. At that time, "the Federal Government held title to approximately 28,000 patents of which fewer than five percent were licensed to companies for commercialization into products." *The Bayh-Dole Act—the Next 25 Years: Hearing Before the Subcomm. on Tech. and Innovation of the H. Comm. on Science and Tech.*, 110th Cong. 12 (July 17, 2007) (prepared statement of Arundeep S. Pradhan) ("Pradhan statement"). In sharp contrast, "[u]niversities . . . which can offer exclusive or partially exclusive licenses on their patents if necessary, ha[d] been able to successfully license 33 percent of their patent portfolios." S. Rep. No. 96-480, at 2 (1979). For that reason, it was understood that "federal government policies that prohibited universities from owning these patents and leasing them to businesses killed the incentives necessary for innovative companies to fully develop these new ideas." Sen. Bayh, *supra*, at 216.

Their proven track record encouraged Congress to grant universities and other nonprofit organizations the right to elect ownership in inventions arising out of federally funded research. Congress's judgment was that nonprofits would be effective cus-

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versity Technology Managers, *AUTM U.S. Licensing Activity Survey: FY 2008*, at 8, *available at* http://www.autm.net/AM/Template.cfm?Section=FY_2008_Licensing_Activity_Survey&Template=/CM/ContentDisplay.cfm&ContentID=4218 (in 2008, universities received $32.7 billion in federal funds, or 63% of total research expenditures).

todians of federal inventions, much as they had been with private inventions. *See* H.R. Rep. No. 96-1307, pt. 1, at 3, *reprinted in* 1980 U.S.C.C.A.N. at 6462.

Congress's judgment has proved prescient. Senator Bayh recently observed that the countless groundbreaking products that have sprung from federally funded research since the Bayh-Dole Act's passage include, as a small sample: "Cisplatin Citracal, [an anticancer agent and] a new treatment for Crohn's disease; recombinant DNA technologies; the nicotine patch; better monitoring of diabetes patients; techniques to reduce infant respiratory deaths; 3-dimensional surgery technologies; new crops; and even the Google search engine." *See* Sen. Bayh, *supra*, at 218. Congress itself has credited the Bayh-Dole Act with numerous other technologies, including "1) Magnetic Resonance Imaging (MRI), which was developed at the University of Wisconsin-Madison; 2) a lithography system to enable the manufacturing of nano-scale devices, which was developed at University of Texas-Austin; and 3) a new effective aneurysm treatment, which was developed at University of California, Los Angeles." H.R. Rep. No. 109-409, at 3 (2006). Other examples include "the Hepatitis B Vaccine (Fox Chase Cancer Center); New Therapeutics for Prostate Cancer (OHSU); [and] New Treatments for Heart Disease (Emory University)." Pradhan statement, 110th Cong. 13; *see also id.* (listing examples from Arizona, California, Oregon, and Nebraska).

Indeed, one recent study of university technology licensing from 1996 to 2007 shows that such licensing contributed $187 billion to the U.S. Gross National Product and $457 billion to gross industrial

output, using conservative models. In addition, university-licensed products commercialized by industry created at least 279,000 new jobs across the United States during the 12-year period. *See* Biotechnology Industry Organization, *The Economic Impact of Licensed Commercialized Inventions Originating in University Research, 1996-2007*, at 6-8 (Sept. 3, 2009), *available at* http://www.bio.org/ip/techtransfer/BIO_final_report_9_3_09 rev_2.pdf. Accordingly, "[d]espite the 'ivory tower' label sometimes attached to U.S. universities, this is now a gross misrepresentation of reality," as "our research universities have been among the most important economic institutions of the twentieth century." *Id.* at 14. In fact, other countries have recognized that "the university-industry collaborations found in the United States [are] a competitive advantage and [have] sought to duplicate the underlying conditions supporting these trends." *Id.*

Petitioner Stanford University has had a fruitful partnership with venture capital firms and innovative startups. For example, Dr. Dari Shalon developed an arraying technique while at Stanford that became the basis of DNA microarray technology. Dr. Shalon decided to launch a startup company called Synteni, and Stanford's Office of Technology Licensing (OTL) granted him an exclusive license to his invention and substantial assistance. The startup attracted $5 million in venture investment from NVCA member Kleiner Perkins Caufield & Byers, and ultimately was sold for $100 million to Incyte Genomics. *See* Intellectual Asset Management, *Licensing in the Boardroom: Key Licensing Issues for Senior*

Executives 14, *available at* http://www.iphandbook.org/jforum/posts/downloadAttach/351.page.

A more familiar example of the fruitful relationship between Stanford and venture capital firms concerns Google, Inc. In the fall of 1995, Sergey Brin and Larry Page began joint work on Stanford's Digital Library Project. That work ultimately led to the development of a search engine, which Brin and Page operated on Stanford's servers and disclosed to OTL in 1996. Two years later, after OTL had explored the possibility of partnerships with several internet companies, Brin and Page proposed to start a company of their own. "OTL discussed the prospect with them and decided Page and Brin would be good stewards of the technology, both because of Page and Brin's expertise and their vision for the technology's development." Rich Scholes, *Uniquely Google(TM)*, Stanford Tech. e-Brainstorm (Mar. 2000), *available at* http://infolab.stanford.edu/pub/voy/museum/google.htm. In June 1999, Google's first press release announced that NVCA members Sequoia Capital and Kleiner Perkins Caufield & Byers had invested $25 million in venture capital. Press Release, *Google Receives $25 Million in Equity Funding* (June 1999), *available at* http://web.archive.org/web/20000309205910/http://google.com/pressrel/pressrelease1.html.

2. The Federal Circuit's decision dismantles the very features of the Bayh-Dole Act that have facilitated the private investment necessary to commercialize inventions arising out of federally funded research.

a. As an initial matter, the Federal Circuit's interpretation of the Bayh-Dole Act undermines what market participants long assumed to be the Act's straightforward and predictable ownership framework. Under the decision below, individual inventors may strip nonprofits of their statutory right to retain ownership of an invention simply by assigning the rights to someone else. If just one co-inventor assigns his rights away—intentionally or otherwise—a nonprofit that subsequently elects to retain title would no longer be the sole owner of the federally funded invention. And if all co-inventors assign away their rights before the nonprofit has had an opportunity to elect title, the nonprofit would then be left with no rights at all.

This uncertainty about ownership necessarily translates into uncertainty about the validity of exclusive licenses. A nonprofit that is not the sole owner of an invention cannot by itself grant a startup company an enforceable exclusive license. *See Ethicon, Inc. v. United States Surgical Corp.*, 135 F.3d 1456, 1468 (Fed. Cir. 1998). And a nonprofit that has no rights to an invention cannot grant a startup company any license at all.

As a consequence, the Federal Circuit's decision would discourage venture capital firms and established companies from investing in federally funded research ideas. If venture capital firms cannot be confident that a startup company holds an enforceable exclusive license, they will be deterred from committing funds to the startup. And if an established company cannot be confident that its own exclusive license is enforceable, it will be deterred from committing its own resources and time. For as Con-

gress recognized when it enacted the Bayh Dole Act, the "private sector simply needs more protection for the time and effort needed to develop and commercialize new products than is afforded by a nonexclusive license." S. Rep. 96-480, at 2.

Little could be done to remove the cloud that the Federal Circuit's decision would cast over licensing agreements. It would not be enough for a licensing nonprofit or licensee startup company to perform a costly investigation into the possibility that any co-inventor might have—perhaps inadvertently—assigned away rights. Given that individual inventors might have assigned *future* inventions long before any invention was conceived (as was the case here), the investigation would need to stretch back decades and exhume long-forgotten contracts. Furthermore, even if it were clear that all existing agreements had been found, the licensing nonprofit or licensee would still need to retain counsel to scrutinize the relationship between the various agreements and assess which agreement takes precedence.

b. The Bayh-Dole Act's ownership framework has been effective not only because it is straightforward and predictable, but also because it makes the universities and nonprofit research institutions—rather than individual inventors—the principal custodians of federally funded invention. As explained, *supra* A.1.b, university funding recipients have proved highly effective at allocating licenses in a manner facilitating the development and commercialization of critical technologies. Additionally, the work experience of the university technology offices ensures that licenses are properly structured and given for

fair compensation (such as equity and royalties) which in turn further supports research in the federally-funded institution. The Federal Circuit's decision would deprive funding recipients of their central role.

Under the Federal Circuit's regime, institutional repeat players, such as the technology transfer offices of universities, would no longer play the leading role in identifying promising companies to which to grant exclusive licenses. Instead, decisions about the ownership of inventions would be made through the ad hoc arrangements, both intentional and inadvertent, of individual researchers. And those decisions would effectively determine whether exclusive licenses could ever be obtained. For example, if four professsor co-inventors unwittingly assigned away their rights to four competitor companies, none of the companies would hold exclusive rights, none could grant an exclusive license, and none would have an incentive to make the substantial investments needed to develop and commercialize raw research ideas.

The Federal Circuit's decision therefore replaces the regime that has operated smoothly for the last three decades with a regime that bears a striking resemblance to the one the Bayh-Dole Act was designed to replace: one in which the uncertainty arising from a "melange of ... different ... policies on vesting of patent rights in government funded research" impeded the formation of risk capital. H.R. Rep. No. 96-1307, pt. 1, at 3, *reprinted in* 1980 U.S.C.C.A.N. at 6462; *see also id.* at 2, *reprinted in* 1980 U.S.C.C.A.N. at 6461.

B. The Federal Circuit's Decision Threatens To Stifle Cooperative Efforts Between Universities And Industry

The Bayh-Dole Act was also designed to encourage cooperative ventures between academia and the business community. *See* 35 U.S.C. § 200 (stating the Act's statutory purpose of "promot[ing] collaboration between commercial concerns and nonprofit organizations, including universities"). In the experience of *amicus*'s members, these cooperative efforts have flourished and been highly productive over the past three decades. The Federal Circuit's decision would threaten to frustrate this collaboration in two ways.

First, the decision below could discourage universities from allowing their faculty to contribute to work at private companies. Because individual professors could undermine a university's statutory right to elect ownership in inventions merely by signing an assignment agreement with a private company, universities may be well advised to limit the opportunities for this to occur.

Universities could, of course, demand that their employees assign them any future inventions before those employees are permitted to enter into cooperative ventures with outside companies. But they could not be confident that a court would give those agreements precedence over individual inventors' subsequent agreements; as this case demonstrates, a university's assignment agreement may be trumped by an individual inventor's later-in-time assignment to a private firm. And even if a university were confident in the primacy of its assignment agreements,

it could still be deprived of the ability to grant exclusive licenses if non-employees were successfully to claim co-inventor status to inventions borne principally out of the work of the university's own employee.

Second, the Federal Circuit's decision could discourage established companies from funding university research, and at a time when federal funding of university research may be decreasing. In the experience of *amicus*'s members, cooperative ventures of this sort have been fruitful in the decades following the enactment of the Bayh-Dole Act. By creating significant uncertainty about the ownership of inventions, however, the Federal Circuit's decision could stifle this cooperation. A company may be dissuaded from granting a university funds for research if were uncertain about the university's rights to inventions arising out of that research—and therefore unable rely on the licensing or assignment arrangements negotiated with the university in connection with the grant of funding.

CONCLUSION

For the foregoing reasons, the Federal Circuit's decision would not only hinder private investment in the process of commercializing federally funded inventions, but also stifle cooperative (and productive) efforts between the business community and universities. The Court should reverse the decision and restore the clarity intended by the Bayh-Dole Act's ownership framework.

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AMICUS CURIAE BRIEF

No. 09-1159

IN THE
Supreme Court of the United States

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AS *AMICUS CURIAE* SUPPORTING RESPONDENT

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INTEREST OF AMICUS CURIAE

The Pharmaceutical Research and Manufacturers of America (PhRMA) is a voluntary, nonprofit association that represents the country's leading research-based pharmaceutical and biotechnology companies.[1] *See* PhRMA Member Company List, *available at* http://www.phrma.org/member_company_list. PhRMA members invested an estimated $45.8 billion in 2009 in discovering and developing new medicines that help patients live longer, healthier and more productive lives. *See* 2010 Pharmaceutical Industry Profile, *available at* http://www.phrma.org/sites/phrma.org/files/attachments/Profile_2010_FINAL.pdf. This amount reflects roughly 70 percent of total pharmaceutical industry spending on research and development. *Id.*

In the conduct of their research, PhRMA members employ researchers, consultants, service providers and other third parties to assist them in inventing and developing new medicines. In connection with these activities, PhRMA members routinely acquire title to all resulting inventions and patents. Such title is important to ensure that any medicines that

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[1] Pursuant to this Court's Rule 37.6, amicus affirms that no counsel for any party authored this brief in whole or in part, that no party or counsel for a party made a monetary contribution intended to fund the preparation or submission of this brief, and that no person other than amicus or its counsel made a monetary contribution intended to fund the preparation or submission of this brief. The parties have consented in writing to the filing of this brief.

are successfully developed will enjoy a sufficient period of market exclusivity to allow them to recoup their research and development expenses, and to provide a return on the developer's investment.

PhRMA members also frequently perform research in collaboration with academic institutions and other entities that receive funding from the federal government. *See id.* These partnerships, and the technology transfer agreements on which they are based, are often an effective way to translate basic research discoveries into commercial medicines while returning significant royalty revenues to academic inventors and their institutions.

Collaborations between academic institutions and PhRMA members almost always involve more than the patent rights of academic inventors. In some cases, inventions by PhRMA members or their collaborators become the subject of later collaborations, and later federal funding. In other cases, PhRMA researchers invent significant improvements that are necessary to convert academic discoveries into commercial products.

The patent ownership issues in this case are important because they have substantial implications for current and future collaborative relationships among PhRMA members, academic institutions, and the government. Intellectual property ownership issues are among the most important, and most carefully negotiated, aspects of technology collaborations. Accordingly, PhRMA's members have a strong interest in the proper interpretation of the Bayh-Dole Act.

SUMMARY OF ARGUMENT

1. The Bayh-Dole Act permits contractors to retain title to their inventions when specified conditions are met, but it does not strip third parties of their ownership or contract rights. By its terms, the Act provides that a contractor may "retain title" to subject inventions. 35 U.S.C. § 202(a). The ordinary meaning of "retain" is to "keep hold of" or "to continue to have." The Bayh-Dole Act thus defines the circumstances in which contractors may continue to hold title to inventions; it does not extinguish the legal rights of third parties or transfer title from third parties to the contractor. The limited scope of the Bayh-Dole Act is confirmed by the statutory definition of a "subject invention" as an "invention of the contractor." 35 U.S.C. § 201(e). Congress knows how to vest title when it wishes to do so; it did not use "vesting" language in the Bayh-Dole Act.

2. This interpretation of the Bayh-Dole Act accords with the expectations of government agencies, universities, and other members of the technology transfer community. The regulations implementing the Bayh-Dole Act provide that the "contractor agrees to require, by written agreement, its employees . . . to . . . execute all papers necessary to . . . establish the government's rights in the subject inventions." 37 C.F.R. § 401.14(f)(2). The NIH has explained that, "[b]y law, an inventor has initial ownership of an invention. However, awardee organizations are required by the Bayh-Dole Act to have in place employee agreements requiring an inventor to 'assign' or give ownership of an invention

to the organization upon acceptance of Federal funds."

Research universities typically require employees to execute patent disclosure and assignment agreements, and frequently advise their employees not to enter into agreements that may conflict with their assignment agreements with the university. These policies reflect an established framework under which universities take active steps to obtain assignments of rights to inventions, and do not rely on the Bayh-Dole Act to strip inventors and other third parties of ownership rights.

Private parties entering into technology transfer agreements with universities do not assume that the university possesses clear title to any federally-funded invention. Instead, leading treatises advise that licensees should obtain a warranty from the university that it is the sole and exclusive owner of the patent rights being licensed. In addition to seeking contractual assurances, parties to technology transfer agreements with universities engage in due diligence to ensure that assignments of rights have been executed by all inventors, employees, and other individuals or business entities.

3. The Bayh-Dole Act seeks to promote collaboration between universities and the private sector, which is vital to innovation and economic growth. Petitioner's proposed interpretation of the Act could jeopardize the continued success of this important and successful collaboration. Private firms may become reluctant to host visitors from academia if in doing so they risk losing title to valuable inventions. Private firms might become less willing to fund university-industry research

centers (UIRCs), which account for roughly half of all industrial funding of academic research in the United States, and could have an incentive to develop research partnerships with foreign universities that are not subject to a "vesting title" regime. The adverse effects of Petitioner's interpretation are likely to be magnified because the Act applies to inventions that are conceived *or* actually reduced to practice in the performance of work under a federal funding agreement, and because even minimal amounts of federal funding may usurp third party ownership rights.

The interests of members of the technology transfer community, and the public interest, are best served by a legal regime that respects contract rights and established principles governing the ownership of inventions. Petitioner's approach would make it difficult or impossible for private parties to negotiate flexible and creative contractual arrangements that create optimum incentives to innovate and bring new technologies to market.

ARGUMENT

I. The Bayh-Dole Act Allocates Title To Inventions As Between The Federal Government And Its Contractors, But Does Not Divest Third Parties Of Title

By its terms, the Bayh-Dole Act applies to inventions of government contractors, and allows contractors to retain their rights to government-funded inventions when specified conditions are met. Petitioner contends that the Act affirmatively *vests* title to inventions in the contractor, even if title would otherwise vest in a third party under patent or contract law. The statutory text does not support Petitioner's interpretation.

The statute provides that a "nonprofit organization or small business may . . . elect to *retain title* to any subject invention." 35 U.S.C. § 202(a) (emphasis added). "Retaining title" is not the same as acquiring title; a contractor cannot "retain" title to an invention it does not already own. *See Oxford English Dictionary* (3d ed. 2010) ("retain" means "[t]o keep in one's own hands or under one's own control; to keep back; to keep hold or possession of; *to continue to have.*") (emphasis added); *Alaska v. United States*, 545 U.S. 75, 104 (2005) (interpreting statute providing that "the United States shall retain title to all property . . ." to mean that "[t]he United States . . . retained title to *its property* located within Alaska's borders") (emphasis added).

If Congress had intended the Bayh-Dole Act to vest title in contractors, it would have used different language to achieve that result. Indeed, the Bayh-Dole Act supplanted several federal "vesting

statutes" that demonstrated Congress's ability to use "vesting" language when it wished to do so. *See, e.g.*, 42 U.S.C. § 2182 (1976) (Department of Energy) ("Any invention or discovery, useful in the production or utilization of special nuclear material or atomic energy, made or conceived in the course of or under any contract, subcontract, or arrangement entered into with or for the benefit of the Commission . . . *shall be vested in*, and be the property of, the Commission."); 42 U.S.C. § 2457(a) (1976) (NASA) ("Whenever any invention is made in the performance of any work under any contract of the Administration . . . such invention *shall be the exclusive property* of the United States, and if such invention is patentable a patent therefor shall be issued to the United States upon application made by the Administrator . . ."); 42 U.S.C. § 5908(a) (1976) (Department of Energy) ("Whenever any invention is made or conceived in the course of or under any contract of the Department . . . title to such invention *shall vest* in the United States . . .") (emphases added). Congress was fully aware of these "vesting" statutes when it enacted the Bayh-Dole Act, and it explicitly recognized that they disposed of rights in subject inventions "in a manner that is inconsistent with this chapter," and stated that Bayh-Dole "shall take precedence over [them]." 35 U.S.C. § 210(a)(6), (7), and (11).

The limited scope of the Bayh-Dole Act is confirmed by the language of § 201(e), which defines a "subject invention" as "any invention *of the contractor* conceived or first actually reduced to practice in the performance of work under a funding agreement . . . ." (emphasis added). If Petitioner

were correct that "the Act confers title to inventions directly upon funded research institutions," Pet. Br. at 30, there would have been no reason for Congress to require that the invention be an invention "of the contractor." *Reiter v. Sonotone Corp.*, 442 U.S. 330, 339 (1979) ("In construing a statute we are obliged to give effect, if possible, to every word Congress used.").

Petitioner and its amici advance two primary textual arguments in support of their contention that the Bayh-Dole Act's conferral of rights is not contingent on a transfer of ownership rights from the inventor to the contractor. *First*, they argue that Section 202(d), which specifies a protocol for the inventor to receive title "[i]f a contractor does not elect to retain title to a subject invention," is the only way in which an inventor can take title to a federally funded invention. *See, e.g.*, U.S. Br. at 7. But Section 202(d) applies only if the Bayh-Dole Act's threshold requirement has been met – *i.e.*, if the invention is an invention "of the contractor," and therefore the contractor has a title that can be "retained." If the contractor has secured the prerequisite title, Section 202(d) specifies the manner in which the inventor may keep the title previously assigned to the contractor. But if the contractor has not obtained an assignment from the inventor, Section 202(d) does not extinguish the inventor's rights.

Second, petitioner and its amici argue that the statement in Section 210(a) that the Bayh-Dole Act gives "precedence" to the Act's "[d]isposition of rights" requires that title automatically vests in the contractor, regardless of the Patent Act's provision that ownership initially vests in the inventor. *See*

U.S. Br. at 8. This argument rests on the false premise that the disposition of inventor's rights contemplated by Bayh-Dole is at variance with other statutes. As discussed above, the Bayh-Dole Act assumes that federally funded contractors have obtained an assignment of ownership rights from the inventor. The Act is thus consistent with long-settled principles of patent law, which recognize that ownership of an invention initially vests in the inventor. *See Gayler v. Wilder*, 51 U.S. 477, 493 (1851) ("[T]he discoverer of a new and useful improvement is vested by law with an inchoate right to its exclusive use, which he may perfect and make absolute by proceeding in the manner which the law requires."); 1 William C. Robinson, *Treatise On The Law Of Patents For Useful Inventions* § 403 at 574 (1890) ("The right of an inventor to a patent vests in him at the moment his invention is completed . . . .").[2]

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[2] The legislative history of the Bayh-Dole Act indicates that Congress was concerned with allocating ownership rights to inventions of the contractor, not with stripping third parties of ownership rights under patent or contract law. *See* 126 Cong. Rec. 1796 (Feb. 5, 1980) (Statement of Sen. Bayh) ("The bill that we are considering today strikes a careful balance, it seems to me, between the rights of the *Federal Government* . . . and the equally important rights of the *inventor and the public* . . . ."); *The University and Small Business Patent Procedures Act: Hearings on S. 414 Before the Sen. Comm. on the Judiciary, 96th Cong.*, 1st Sess. 97 (1979) (Statement of Patrick Iannotta, President, Ecolotrol Inc.) ("Frankly, it was a very frustrating experience trying to deal with the Government. (continued...)

II. The Court of Appeals' Decision Accords With The Settled Expectations Of Government Agencies, Universities, And Third Parties

Petitioner contends that the court of appeals' decision disrupts a settled framework guaranteeing a research contractor clear title to a federally funded invention, regardless of competing ownership claims. Pet. Br. 45-48. As discussed below, there is no such settled framework. To the contrary, government agencies, universities, and other members of the technology transfer community all recognize that the inventor's title to an invention must be properly assigned to the contractor in order for a contractor to retain rights under the Bayh-Dole Act.

A. Federal Agencies Recognize That Contractors Cannot Retain Title Under The Bayh-Dole Act Without Assignments From Inventors

Under 35 U.S.C. § 206, the Secretary of Commerce is authorized to implement the Bayh-Dole Act, and to promulgate standard contract clauses for funding agreements. The Secretary's regulations and contract clauses are codified at 37 C.F.R. § 401. Section 401.14, which provides "standard patent rights clauses" to be used by agencies in their funding agreements, obligates the funding recipient

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After all, *all we were trying to do was to protect what we already owned.*") (emphases added).

to execute written assignments from inventors of funded inventions:

> The contractor agrees to require, by written agreement, its employees . . . to . . . execute all papers necessary to file patent applications on subject inventions and to establish the government's rights in the subject inventions.

37 C.F.R. § 401.14(f)(2). If the Bayh-Dole Act automatically vested title in the contractor, it would not be necessary for contractors to obtain "written agreement" from their inventor employees to "establish the government's rights."

Petitioner argues that the statement in § 401.14(a)(1) that "[t]he Contractor may retain the entire right, title, and interest throughout the world to each subject invention," "cannot be squared with a view that Bayh-Dole determines only the disposition of rights between the Government and the institution." Pet. Br. at 43. But Petitioner omits key language from the regulation, which specifies that the contractor's rights are "subject to the provisions of this clause." 37 C.F.R. § 401.14(b). Those provisions include the requirement that the contractor obtain the "written agreement" of employee inventors to "execute all papers necessary . . . to establish the government's rights."

Bayh-Dole compliance guidelines published by the National Institutes of Health (NIH) confirm this understanding. In a section entitled "20 INVENTION REPORTING TERMS WITH WHICH

EVERY NIH AWARDEE SHOULD BE FAMILIAR," the very first paragraph informs contractors:

> 1. ASSIGNMENT.
>
> Transfer of title or ownership in patent rights in the form of a written assignment document. *By law, an inventor has initial ownership of an invention. However, awardee organizations are required by the Bayh-Dole Act to have in place employee agreements requiring an inventor to "assign" or give ownership of an invention to the organization* upon acceptance of Federal funds.

NIH Policies, Procedures, and Forms, *A '20-20' View of Invention Reporting to the National Institutes of Health, available at* https://s-edison.info.nih.gov/iEdison/twenty_questions_updated.jsp (Adapted and updated from: 24 NIH GUIDE 33, Sept. 22, 1995) (emphasis added). Given its annual budget of over $30 billion,[3] and its position as the nation's "largest funding agency for biomedical research,[4] NIH's views merit careful consideration.

In sum, the regulations and the NIH guidelines both reflect the understanding that the contractor's duty to secure ownership rights from the inventor is

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[3] *NIH Budget, available at* http://www.nih.gov/about/budget.htm.

[4] Benn Steil, et al., *Technological Innovation and Economic Performance*, 362 (2002).

a prerequisite to enjoying the benefits of the Bayh-Dole Act.

B. Research Universities Do Not Assume That The Bayh-Dole Act Automatically Confers Title On Contractors

Petitioner and its university amici contend that the court of appeals' decision will require them to begin performing "wide-ranging inquir[ies] on subject inventions" to search for "unknown prior assignment[s] by a named inventor," and that such diligence will "significantly increase [their] administrative costs." Pet. Br. at 46-47; *see also* Brief of The Association Of American Universities, et al. ("AAU Br.") at 31-32 (decision "undermines the certainty of university title that is central to Bayh-Dole's success," and "re-injects uncertainty into the commercialization of federally funded inventions."). These contentions are belied by assignment policies and procedures that are already in place at a broad spectrum of research universities.

Most universities have written intellectual property policies in their faculty/staff handbooks that claim ownership of inventions derived using university resources. *See* G. Kenneth Smith, *Faculty And Graduate-Student Generated Inventions: Is University Ownership a Legal Certainty?*, 1 Va. J. L. & Tech. 4 (1997). Pursuant to these policies, universities generally require new hires to sign patent disclosure and assignment agreements as a condition of employment. *See id.*

Academic institutions take affirmative measures to require their employee inventors to execute

written assignments. *See, e.g.*, Yale University *Patent Policy* (February, 1998), *available at* http://www.yale.edu/ocr/pfg/policies/patents.html ("Inventors shall execute assignments or other documents assigning to the University all their rights in the invention and any patent applications or resulting patents on the invention. Yale will retain title to all such patent applications and resulting patents."); Duke University *Policy on Inventions, Patents, and Technology Transfer* (1998), *available at* http://olv.duke.edu/Inventors/PoliciesAndProcedures/policy_on_inventions.pdf ("Inventions resulting from research or other work conducted by university employees in whole or in part on university time or with significant use of university funds or facilities shall be considered the property of the university. Employees shall upon request assign to the university all rights and title to such inventions and shall make known and available to the university all supportive technology related to the same."); Cornell University *Inventions and Related Rights Policy Statement 1.5* (July, 1995), *available at* http://www.dfa.cornell.edu/dfa/treasurer/policyoffice/policies/volumes/academic/inventions.cfm ("All inventions made by an individual with (i) a university appointment in furtherance of his/her university responsibilities, and/or (ii) with the use of university resources, including those provided through an externally funded grant, contract, or other type of award or gift to the university, belong to the university. . . . If [Cornell] determines that Cornell has an ownership interest, the inventor must assign all rights and titles of the invention to the university or its designee . . . .").

Indeed, Petitioner's own patent policy takes this approach. *See* Stanford University *Research Policy Handbook*: *Inventions, Patents, and Licensing (RPH 5.1)* (July 15, 1999), *available at* http://rph.stanford.edu/5-1.html ("All potentially patentable inventions conceived or first reduced to practice in whole or in part by members of the faculty or staff (including student employees) of the University in the course of their University responsibilities or with more than incidental use of University resources, shall be disclosed on a timely basis to the University. Title to such inventions shall be assigned to the University, regardless of the source of funding, if any.").

Several universities explicitly acknowledge a nexus between their Bayh-Dole duties and the need for inventors to execute written assignments. For example, Yale University's patent policy states:

> Current governmental regulations permit educational institutions to retain rights and title to patentable inventions which results from federally funded experimental, developmental and research work. *Retention of rights by University is contingent upon the fulfilling of a number of obligations on the part of the University and of the Inventor(s)* and these obligations must be discharged in order to protect the interests of all parties. . . . *Incumbent upon members of the University community who apply for and receive federal funding to support research or who use federal monies in the conduct of*

> *their research is the requirement for written agreement that they will promptly disclose patentable inventions to the University and will execute all instruments necessary to protect the rights of the government and/or the University.*

Yale University Patent Policy at ¶ 9. Similarly, the University of California system advises faculty at its affiliated universities that the university is "obligated to have written agreements with its faculty and technical staff requiring the disclosure and assignment of inventions." University of California, Technology Transfer, *The Bayh-Dole Act: A Guide To The Law And Implementing Regulations* (1999), *available at* http://www.ucop.edu/ott/faculty/bayh.html#FN4a.

Universities also routinely allow their faculty to consult with private enterprise, commonly advise their employees not to enter into agreements that would conflict with the employees' assignment agreements with the university, and employ procedures to clear any potential conflicts that may arise. The policy of the Massachusetts Institute of Technology ("MIT") is typical:

> It is the responsibility of individual members of the MIT community to ensure that the terms of their consulting agreements with third parties do not conflict with their commitments to the Institute . . . . Each individual should make the nature of his or her obligations to the Institute clear to any third party for whom he or

> she expects to consult. Specifically, the scope of the consulting services should be distinguished from the scope of research commitments at the Institute.

MIT *Policies & Procedures*, § 13.1.5, *available at* http://web.mit.edu/ policies/13/13.1.html. Similarly, the Johns Hopkins University requires faculty members to obtain clearance from the university before entering into consulting agreements, in recognition that such agreements can clash with "[u]niversity policies" and "government regulations":

> In cases where faculty enjoy rights to Intellectual Property under this policy, they have an obligation to report fully any outside activities and interests related to their teaching, research, or service to their Department Chair, Dean or other designated University official and obtain their prior approval before the activity begins. The report must be in writing and must include the names of companies for whom he/she consults, the number of days committed to each consulting agreement and a copy of any proposed consulting agreements associated with Intellectual Property. Consulting agreements must be reviewed for compliance with University policies and government regulations and approved by the appropriate Divisional office before the *consultation can begin*.

The Johns Hopkins University *Intellectual Property Policy*, § VI E 2, (April 2, 2001) *available at*

http://jhuresearch.jhu.edu/JHU_Intellectual_Property_Policy.pdf (emphasis added).

These policies reflect an established framework under which universities take active steps to minimize the risk that employee inventors might jeopardize Bayh-Dole title rights. The court of appeals' decision thus accords with existing expectations in the technology transfer community, by holding that title under the Bayh-Dole Act is not automatically vested, but instead is "retained." *See* Homer A. Neal et al., *Beyond Sputnik: U.S. Science Policy In The Twenty-First Century* 107 (2008) ("Bayh-Dole requires universities to obtain written agreements from faculty and research staff committing that they will assign IP ownership to the institution."); Stephen Fishman, *What Every Inventor Needs To Know About Business & Taxes* 23 (2d ed. 2005) ("The Bayh-Dole Act works like this: . . . The university must have written agreements with its faculty and technical staff requiring disclosure and assignment of inventions.").

C. Universities Entering Into Technology Transfer Agreements Frequently Provide Warranties That They Have Secured Assignments From Inventors

According to some of Petitioner's amici, research agreements between universities and private industry prior to the Federal Circuit's decision have assumed that clear title to federally funded inventions belonged to universities. *See, e.g.*, AAU Br. at 24-25 (sponsored research agreements "start with the premise that the university will have the

right under Bayh-Dole to . . . license the inventions"); Brief of National Venture Capital Association at 6-7 ("a startup company holding an exclusive license from a university, for example, could easily prove that the ownership of its license was valid simply by pointing to its agreements with the university. No further inquiry or investigation was required.").

Contrary to these contentions, an assumption that universities own clear title to federally funded inventions is contrary to widely-followed best practices applied to technology transfer agreements. One of the primary assurances sought by participants in technology licensing transactions is a warranty that the university has clear title to the transacted invention. A leading treatise on technology transfer agreements, in a "Model Exclusive License Agreement Conforming to Stevenson-Wydler and Bayh-Dole Act Licensing Restrictions" lists the following as the *very first* warranty and disclaimer to be sought from a university:

> A. The UNIVERSITY warrants that it is the lawful owner of the PATENT RIGHTS identified in paragraph 1.B above.

Michael J. Lennon, *Technology Transfer Guide* (Lennon) § 6.03[G] at 6-96 (Supp. 2001); *see also* Lennon § 9.02 at 9-7-8 (2000) ("REPRESENTATIONS, WARRANTIES, AND COVENANTS OF THE OWNER-LICENSOR IN TECHNOLOGY TRANSFER TRANSACTIONS . . . The licensor should warrant that the inventorship in the licensed patents resides solely and exclusively in the named inventors."). Such a warranty would be

unnecessary if the Bayh-Dole Act automatically vested title in federal contractors.

Industrial participants in transactions with universities also seek assurances that licenses to funded inventions are sufficient, standing alone, to allow commercialization:

> Warranties and Representations for Agreements with Academic Institutions
>
> The UNIVERSITY represents and warrants to the LICENSEE that, as of the Effective Date of this Agreement:
>
> a) The LICENSEE does not need any license or right which is owned by the UNIVERSITY not already granted under the terms of this Agreement that is necessary or useful for the LICENSEE and its affiliates to manufacture and use the Licensed Intellectual Property Rights.

Id. § 5.10 at 5-16-17.[5] Another leading treatise advises industrial collaborators to exercise similar caution:

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[5] The Lennon treatise further advises:

> The representations and warranties of the parties to a technology transfer transaction guarantee the underlying assumptions of the agreement, for example, that the licensor has unencumbered title to the technology and has the right to grant the licenses conveyed to the licensee to commercialize it.

(continued...)

> REPRESENTATION BY INSTITUTION REGARDING PROPRIETARY POSITION
>
> Institution represents that Institution is not party to any agreement which in any way restricts Institution's power to convey by assignment or license agreement rights to Inventions and Know-How in the Field which may be conceived under this Research Agreement . . .

Michael Epstein & Frank L. Politano, *Drafting License Agreements* 26-159 (4th ed. 2004) (in appendix entitled "Model Provisions For Licenses And Sponsored Research Contracts Involving Academic Institutions"). These negotiated provisions would be unnecessary if industrial participants could rely upon the vesting of title under the Bayh-Dole Act.

In addition to seeking contractual assurances from universities, parties to technology transfer agreements engage in due diligence efforts to ensure that transacted patents carry clear title. According

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> The basic clauses normally state that the licensor is the exclusive owner of the technology, has the right to grant the licenses conveyed, and is not aware of any conflicts with the rights of third parties that would be created by the conveyance of these licenses from the licensor to the licensee.

Id. § 4.01[P] at 4-34.

to one leading authority, the first due diligence task for a company seeking to license a university patent is to seek an answer to the following question: "Have assignments of the rights to be transferred been executed by all inventors, employees, and any other individuals or business entities so that ownership, and the licensee's right to use the licensed technology, will not be disputed?" Lennon § 9.01[A] at 9-3. Parties to technology transfer agreements are well aware that "[w]ithout clear title vested in the licensor or assignor, the licensee or assignee may not receive the rights bargained for." *Id.* Again, these efforts would be unnecessary if the parties understood that the Bayh-Dole Act automatically vested title in the university.

III. The Public Interest Is Served By Affirming The Court Of Appeals' Decision

A. An Expansive Interpretation of Bayh-Dole May Jeopardize Collaboration Between Universities And Third Parties

Collaboration between universities and the private sector is vital to innovation and economic growth in the United States. Between 1980, when Congress enacted the Bayh-Dole Act, and 2000, funding from private industry for science and engineering research at universities doubled, from four percent to almost eight percent of total university research dollars. Amy Zusman, Challenges Facing Higher Education In The Twenty-First Century, *in American Higher Education In The Twenty-First Century: Social, Political, and Economic Challenges* 124 (Philip G. Altbach et al.

eds., 2005). Most life scientists agree that "research support from industry 'provides resources for research that could not be obtained elsewhere' and 'involves less red tape than federal funding.'" Karen Seashore Louis & Melissa S. Anderson, The Changing Context of Science, in Capitalizing Knowledge: New Intersections of Industry and Academia 79 (Henry Etzkowitz et al. eds. 1998).

Pharmaceutical companies view collaborative arrangements with universities as a "source of discoveries leading to new products." Panel on the Gov. Role in Civilian Tech., Comm. on Sci., Eng'g, & Pub. Policy, Nat'l Acad. of Scis., et al., *The Government Role in Civilian Technology: Building A New Alliance*, 165 (1992). The relationship between industry and academia enables basic science research to be converted into applied technology that is useful to society. *See, e.g.*, Stuart O. Schweitzer, *Pharmaceutical Economics And Policy* 31-32 (2007) ("Often academic researchers who receive government research grants and contracts have direct connections to the private sector. . . . These relationships can be viewed as useful linkages between the 'theoretical' world of academia and the 'practical' world of industry."). As one commentator has observed, "Bayh-Dole is widely viewed as having created incentives for socially useful collaboration between academia and industry. The resulting commercialization of research harnesses the collective intellectual and creative talents of university faculty, speeds the development of new and improved therapies, stimulates regional economic growth, and contributes to the economic viability of research institutions." Shaili Jain,

Understanding Physician-Pharmaceutical Industry Interactions: A Concise Guide 94 (2007).

The continued success of partnerships between academia and private industry may be placed at risk if, as Petitioner contends, title to inventions automatically vests in federally funded universities, irrespective of prior contractual agreements. For example, private firms may be reluctant to host visitors from academia like Dr. Holodniy if, regardless of their efforts to secure rights over inventions arising from such collaboration, universities are later able to play a Bayh-Dole "trump card" that grants them title. More generally, if private firms cannot rely on written agreements to guarantee their rights in inventions resulting from collaborative arrangements with academia, the incentives to pursue such collaborations will be diminished.

The adverse effects of Petitioner's interpretation of the Bayh-Dole Act would be magnified because the Act applies to inventions that are conceived *or* first actually reduced to practice in the performance of work under a funding agreement. 35 U.S.C. § 201(e). Thus, even if an invention is first conceived by an inventor working in the private sector without any government funding and is *constructively* reduced to practice through the filing of a patent application, the university could still acquire ownership of the invention under Petitioner's interpretation if it was first *actually* reduced to practice at the university in the performance of work under a funding agreement. This outcome contravenes the settled framework of 35 U.S.C. § 102(g). *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986)

("constructive reduction to practice occurs when a patent application on the claimed invention is filed"); *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577 (Fed. Cir. 1996) ("the person who first reduces an invention to practice is 'prima facie the first and true inventor.'") (quoting *Christie v. Seybold*, 55 F. 69, 76 (6th Cir. 1893) (Taft, J.)). Moreover, Petitioner and its amici do not suggest that any minimum threshold of federal funding is necessary to trigger ownership rights under Bayh-Dole. In the absence of such a threshold, even a minimal amount of federal money risks "contaminating" privately-sponsored research, an interpretation that raises Fifth Amendment implications.

Concerns about "contamination" apply with added force to university-industry research centers (UIRCs). Such centers, which account for roughly half of all industrial funding of academic research in the United States, allow industry and academia jointly to define research portfolios, facilitate industry access to university basic science research, and promote transfer of technology to the marketplace. *See* Fraunhoffer Institute for Systems and Inovative Research, National Academy of Engineering, *Technology Transfer Systems In The United States and Germany: Lessons and Perspectives* 18 (H. Norman Abramson et al. eds., 1997). A 1994 study of over one thousand UIRCs showed that these centers received funding in excess of $4.12 billion, and involved 12,000 university faculty and 22,300 doctoral-level researchers. Wesley Cohen et al., *University-Industry Research Centers in the United States* (1994). At most UIRCs, support from private industry is matched by funding from federal

government entities. *Id.* The continued viability of UIRCs could be threatened by an interpretation of the Bayh-Dole Act that allows universities to assert sole title to inventions whenever private funds are combined with federal funds.

Faced with a legal regime in which universities can invoke the Bayh-Dole Act to obtain sweeping ownership rights, private firms may be encouraged to develop research partnerships with foreign universities based in countries that do not allow government contractors to claim title in inventions to which they have no contractual rights. Any such development could have negative consequences, including reducing the competitiveness of American institutions of higher learning and stemming the flow of talented foreign students to the United States.

B. The Public Interest Is Furthered By Respect For Contractual Agreements

The public interest, and the interests of members of the technology transfer community, are best served by respecting contract rights and well-established principles concerning ownership of inventions and transfer of those rights by assignment.

Ownership of an invention inures in the inventor, unless and until assigned. 35 U.S.C. §§ 101, 261 ("[w]hoever invents or discovers a new and useful [invention] may obtain a patent therefore"; patents are "assignable in law by an instrument in writing"). Under Petitioner's interpretation of the Bayh-Dole Act, universities can divest inventors and their

assignees of title to their inventions merely by invoking federal funding.

For example, assume that a researcher who does not receive any federal funding conceives of an invention while working for a private company. Pursuant to the inventor's contractual agreement with the company, all rights to the invention belong to the company. The company files a patent application on the invention, thereby constructively reducing the invention to practice. Thereafter, the researcher is hired away by a university, where the invention is first actually reduced to practice. It later comes to light that a small amount of federal grant money was used in the actual reduction to practice. On that basis, the university claims ownership of the invention under the Bayh-Dole Act. The university could assert such a claim, in Petitioner's view, even if the researcher had never entered into an assignment agreement with the university (and even if the assignment agreement between the researcher and the university expressly excluded the invention at issue).[6]

These results are inappropriate. Universities, private companies, and employees all benefit by defining their respective rights through explicit agreements. If the right of employee-inventors to

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[6] Similarly, under Petitioner's view, if two research teams are engaged in independent, parallel research efforts, the government-funded team that first actually reduces an invention to practice could claim exclusive ownership rights even if the invention was first conceived and constructively reduced to practice by the private research team.

control disposition of their inventions is curtailed, the incentive for those employees to innovate (and to work for recipients of federal funds) may be weakened.

The Federal Circuit's holding encourages universities and private industry to enter into contracts that determine their respective rights in collaborative arrangements. As discussed above, private parties are well equipped to navigate contractual issues and further their interests through negotiated agreements. Flexible contractual arrangements allow technology transfer participants to establish incentives for the mutual benefit of all parties. Petitioner's approach, in contrast, would make it difficult or impossible for private parties to negotiate flexible and creative arrangements that create optimum incentives to innovate and bring new technologies to market. That result is detrimental to the public interest and contrary to the purpose of the Bayh-Dole Act, which seeks "to promote collaboration between commercial concerns and nonprofit organizations, including universities." 35 U.S.C. § 200.

CONCLUSION

The judgment of the court of appeals should be affirmed.

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AMICUS CURIAE BRIEF

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IN THE SUPREME COURT OF THE UNITED STATES

BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC., ET AL.

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR ALEXANDER M. SHUKH, PH.D. AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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QUESTION PRESENTED

Whether a federal contractor university's statutory right under the Bayh-Dole Act, 35 U.S.C. §§ 200-212, in inventions arising from federally funded research can be terminated unilaterally by an individual inventor through a separate agreement purporting to assign the inventor's rights to a third party.

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INTERESTS OF *AMICUS CURIAE*

Dr. Alexander M. Shukh is one of the world's leading inventors and engineers of hard drive disk technology, one of the most advanced fields of scientific endeavor known to humankind.[1] He files this Brief in support of Petitioner.

He holds a Ph.D. (1983) in Physics and Mathematics with specialization in Condensed Matter Physics from the Institute of Electronics, Belarusian Academy of Sciences, Minsk, Belarus; an M.S. (1980) in Electrical and Electronics Engineering, Minsk Radio Engineering Institute, Minsk, Belarus; and a B.S. (1976) in Electrical and Electronics Engineering, Minsk Radio Engineering Institute, Minsk, Belarus.

Since October 1976, he has worked as a scientist, development engineer, manager, director and associate professor in the field of magnetic recording heads, giant magnetoresistance transducers, magnetic media, thin film and semiconductor circuits.

Either as sole or joint inventor, he has been awarded twenty United States Patents,[2] fifteen issued patents of the former Soviet Union, and is currently listed on

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[1] Pursuant to Rule 37.6, counsel for *amicus* states that no counsel for a party authored this brief in whole or in part and no person, other than *amicus*, its members, or its counsel made a monetary contribution to the preparation of this brief. The parties have filed consents to the filing of *amicus* briefs in support of either party or no party.

[2] *USPTO Patent Full-Text and Image Database*, available at http://patft.uspto.gov/netahtml/PTO/search-bool.html (Search "Shukh" and "Choukh" in "Inventor" field).

several pending United States patent applications. He is the author of at least thirty-nine published papers, and has regularly made presentations at important conferences in his areas of research and R&D interest.

He emigrated to the United States in September 1997 under a temporary foreign worker H1-B work authorization visa when he became employed at the Bloomington, Minnesota research facility of Seagate Technology, Inc., a well-known hard disk drive manufacturer. On May 30, 2002, he received his United States Permanent Resident Card (Green Card) and became a Lawful Permanent Resident of the United States.

He was employed by Seagate from September 1997 until March 16, 2009.

His work at Seagate resulted in the issuance of numerous patents for inventions or co-inventions related to Seagate's business as a hard drive manufacturer.

He is a Member of the Seagate Inventor Hall of Fame as a result of his invention of more than ten patented inventions while at Seagate.

Nine of his inventions have been incorporated into several Seagate product lines of hard disk drives and related products and have been included into several hundred million (probably closer to 1.2 billion) hard disk drive units sold by Seagate in the national and international hard drive market. Currently, up to five of his inventions are in each disk drive unit made by Seagate.

Dr. Shukh became a United States Citizen on July

30, 2009.

He is the plaintiff in the case of *Alexander M. Shukh, Ph D. v. Seagate Technology, LLC*, Case No. 10-cv-404-JRT-JJK (D. Minn.) (filed on Feb. 12, 2010 under seal). In part, his case involves issues related to the invention assignment provisions contained in the Employment and Invention Assignment Agreement he signed in 1997 upon his employment with Seagate. Dr. Shukh alleges that during his employment at Seagate, as a co-inventor he conceived and reduced to practice certain inventions, but that when Seagate applied for patents on those inventions, it did not disclose his co-inventorship and did not obtain and file his inventor's oath as required by Patent Act Sections 111, 115 and 116 of the Patent Act, 35 U.S.C. §§ 111, 115, 116. Nor did he give Seagate the assignment which Section 3.73 of the Patent Office's Manual of Patent Examination Procedure, 37 C.F.R. § 3.73, required be filed for Seagate to prosecute those applications. Thus, among other relief, Dr. Shukh is seeking correction of inventorship pursuant to 35 U.S.C. § 256, and a declaration of co-ownership of the patents.

The provisions in Dr. Shukh's Employment-Assignment Agreement are closely akin to those in the agreements in this case that Dr. Holodniy signed first with Stanford University and then with Cetus Corporation. His case and situation, however, do not involve the application of the Bayh-Dole Act.

Dr. Shukh wishes to provide the Court with the perspective of an inventor in the critically important and quickly evolving American computer technology industry regarding the Federal Circuit's misdirected jurisprudence about the interpretation of invention

assignment provisions in general. He is concerned that, unless corrected, the Federal Circuit rules of construction of such invention assignment provisions, especially in non–Bayh-Dole Act situations, will seriously degrade the Constitutional Purpose of the Patent and Copyright Clause of Article I, Section 8 of the Constitution, disrupt settled expectations of inventors about their rights of inventorship, annul provisions of the Patent Act and Patent Office regulations that govern the ownership of patents and the process of applying for and obtaining those patents, and thereby allow inventors to be stripped of their inventorship and ownership rights.

CONSTITUTIONAL PROVISION, STATUTE AND REGULATION INVOLVED

Dr. Shukh believes that this case also involves the following Constitutional Provision, Statute and Regulation:

United States Constitution, Article I, Section 8.

Section 261 of the United States Patent Act, 35 U.S.C. 261 "Ownership; assignment."

Section 3.73 of the Manual of Patent Examination Procedure, 37 C.F.R. § 3.73, "Establishing right of assignee to take action."

The text of those provisions is set out in the Appendix to this Brief.

STATEMENT

On June 28, 1988, when Dr. Holodniy signed the Stanford agreement that contained the "***agree to assign or confirm in writing***" language, Pet. App. 119a. (emphasis added), the inventions that are the

subject of this lawsuit had not been conceived or reduced to practice and therefore did not exist.

Likewise, those inventions did not exist, when, about seven months later, Dr. Holodniy signed the Cetus agreement containing the "***I will assign and do hereby assign***" language. Pet. App. 123a. (emphasis added.)

In fact, it was not until 1991 that the inventions at issue were conceived, reduced to practice, and therefore came into existence. Pet. App. 5a, 39a-40a.

On May 14, 1992, Stanford filed Patent Application No. 07/883,327 for those inventions. Pet. App. 3a-4a, 40a. That Application was the parent application of the three patents in suit. Pet. App. 126a, 128a, 132a.

In early March 1995, long before any of the patents issued, Dr. Holodniy and his co-inventors executed an assignment of the inventions covered by that parent application. That assignment was recorded with the Assignment Division of the Patent Office on June 9, 1995, also long before any of the patents issued. (Ex. 705 to Decl. of M. Rhyu in Support of Pls.' Opp. to Defs.' Mot. for Summ. J., [D. Ct. Dkt. No. 113-8]; *see also* Pet. App. 41a, 112a.)

On their face, all three patents as issued reflected that Stanford was the assignee. Pet. App. 125a, 127a, 131a.

There are no documents of title by any inventor or anyone else transferring any interest in the patents to Cetus or its successor, respondent Roche Molecular Systems, Inc.

The current online Patent Office records reflect that

Stanford, not Roche, is the assignee of the three patents at issue, although this may only be a designation of the assignee at the time the patents issued.[3]

SUMMARY OF ARGUMENT

There is no principled difference between assignment provisions that say "I hereby assign" or "I will assign." They should be treated as equivalent, and should be construed to grant equitable title that must be perfected by a subsequent act transferring title.

The importance of this issue cannot be overstated, given the enormous number of patents likely affected by the court of appeals' artificial rule, including the important patents resulting from federally funded research that are subject to the Bayh-Dole Act.

The Federal Circuit's nonsensical "present/future" assignment dichotomy is contrary to a significant purpose of the Constitution's Patent Clause of protecting the inventorship rights of inventors.

The Panel's rationale is suspect on its face. Its illogical and impractical treatment of the competing equitable rights of the parties creates serious anomalies of ownership that, when extended beyond this case, will surely cloud title of a vast number of patents.

Traditional rules of equity and modern-day contract

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[3] *USPTO Patent Full-Text and Image Database* available at http://patft.uspto.gov/netahtml/PTO/search-bool.html (last visited December 21, 2010 – Search by Patent Number: 7,129,041, 6,503,705, and 5,968,730 in "Patent No." field.)

law have always recognized that non-existent personal property cannot be automatically or immediately assigned in the present, and that at most such a purported assignment transfers only equitable title which must be perfected by a subsequent instrument transferring ownership.

Beginning with *Gayler v. Wilder*, 51 U.S. (17 Wall.) 477, 493 (1850), prior decisions of this Court reflect the common sense rule that future interests in patents can be assigned only if there is an "inchoate right" to that assignment and a "power" to enforce it.

The Federal Circuit's strained dichotomy has grave deleterious effects on the rights of inventors, as well as competing assignees such as petitioner and respondent, simply because in balancing claims of ownership to newly created inventions, that dichotomy eliminates the consideration of the equities, including the public interest, that are likely to intervene in the period between the execution of the assignment agreement and the creation of a new invention.

There are important policy reasons supporting the construction that agreements to assign future inventions convey only equitable title which must be perfected when the invention comes into existence. This is in full accord with well-established Patent Office regulations and practice that require a patent applicant to document its ownership of an invention for which it is prosecuting a patent application.

The equitable title regime advocated by *amicus* aligns comfortably with the purpose and structure of the Bayh-Dole Act. It would be unwise to create conflicting regimes of invention assignment law, one

for the Bayh-Dole Act context, and another applicable to private invention assignment agreements.

The rule that should be adopted in this case is that no matter how worded, an assignment of a future, as yet unconceived, invention transfers only equitable title requiring an additional act to transfer legal title and ownership once the invention comes into existence.

ARGUMENT

Because of the confusion and disarray that the Federal Circuit's decision introduces into Patent Law, especially insofar as it seriously impairs the rights of inventors, this Court should step in and rationalize the rules relating to inventor assignment agreements.

A NON-EXISTENT INVENTION CANNOT BE AUTOMATICALLY OR IMMEDIATELY ASSIGNED IN THE PRESENT.

As a matter of common sense, there cannot be a present, automatic or immediate assignment of an invention that does not exist. But under the Federal Circuit's rule, when an inventor executes a "hereby assigns" agreement regarding his or her future inventions, ownership of that non-existent invention supposedly immediately transfers to the assignee.

This cannot be so.

A. The Context of this Case Extends Beyond the Important Issues of Patent Ownership Arising from Federally Funded Research.

The importance of this case extends beyond the difficult issues under the Bayh-Dole Act related to ownership of patents resulting from federally funded

research. Pet., pp. 2,4.

This case also presents critical questions about the rights of inventors to their inventions and the resulting patents, and the methods, procedures and rules by which an inventor's initial ownership should be transferred.

Therefore, the number of patents affected by the resolution of this case is enormous. Patent Office statistics show that of the 167,349 utility patents granted in 2009, only 19,894 (11.9%) were issued to individual inventors at the time of grant; the rest were granted to organizations.[4] Indeed, it is generally accepted that "the great majority of contemporary inventors create new technologies while serving as employees, usually of large corporate entities." Roger Schechter & John Thomas, *Principles of Patent Law* (2d ed. 2004); *see also Ingersoll-Rand Co. v. Ciavatta*, 110 N.J. 609, 624, 542 A.2d 879, 886 (1988). Thus, rules of construction of invention assignment agreements between inventors and their employers reach far beyond the realm of federally funded research and the Bayh-Dole Act.

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[4] Compare: U.S. Patent and Trademark Office Patent Technology Monitoring Team Statistical Reports – *Patent Counts By Class By Year – Independent Inventors*, www.uspto.gov/web/offices/ac/ido/oeip/taf/clscby_in.htm with *Table of Annual U.S. Patent Activity Since 1790* www.uspto.gov/web/offices/ac/ido/oeip/taf/h_counts.htm (both last visited Dec. 21, 2010). *See also, id.*, Patenting Trends Calendar Year 2009 (Apr. 16, 2010), stating percentage of all types of patents granted to individuals. www.uspto.gov/web/offices/ac/ido/oeip/taf/pat_tr09.htm (last visited Dec. 21, 2010).

Stanford is one of the world's leading research universities, and is likely a recipient of tens of millions of dollars of federal funds for research. Patent Office statistical reports show that from 2005 to 2009, 503 issued patents were assigned to Stanford.[5] All of those patents are now at risk if its inventor assignment agreements say "agree to assign" rather than "hereby assign."

Just as seriously, this artificial dichotomy is a trap for the unwary inventor whose transfer of ownership of newly created inventions should be evaluated in terms of events, equities and rights that might arise in the gap, sometimes years in length, between the initial execution of the assignment agreement and the conception, reduction to practice, and patenting of the invention. After all, it is the inventor that is the object of the protections of the Constitution's Patent Clause.

B. The Decision Below is Suspect on its Face.

The Panel below reached back to what seems to be the first Federal Circuit decision stating the dichotomy between present and future invention assignments, and its progeny. *FilmTec Corp. v. Allied-Signal, Inc.*, 939 F.2d 1568, 1572-73 (Fed. Cir. 1991), Pet. App 12a-14a. *See also DDB Techs., L.L.C. v. MLB Advanced Media, L.P.*, 517 F.3d 1284, 1290 (Fed. Cir. 2008) ("agrees to and does hereby grant and assign" is language of present assignment); *IpVenture, Inc. v.*

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[5] *Id., Patenting In Technology Classes, Breakout By Organization Count of 2005 - 2009 Utility Patent Grants*, www.uspto.gov/web/offices/ac/ido/oeip/taf/tecasg/all_tor.htm (last visited Dec. 21, 2010).

Prostar Computer, Inc., 503 F.3d 1324, 1327 (Fed. Cir. 2007) (interpreting "agree to assign" as "an agreement to assign," requiring a subsequent written instrument); *Speedplay, Inc. v. Bebop, Inc.*, 211 F.3d 1245, 1253 (Fed. Cir. 2000) (interpreting "shall belong" as a present assignment); *Arachnid, Inc. v. Merit Indus., Inc.*, 939 F.2d 1574, 1580-81 (Fed. Cir. 1991) (holding that "will be assigned" does not create "a present assignment of an expectant interest").

On the basis of this line of authority, the Panel held that the "hereby assign" language of the Cetus agreement "effected a present assignment of Holodniy's future inventions to Cetus," Pet. App. 14a, while in contrast, his agreement with Stanford was only "a mere promise to assign rights in the future, not an immediate transfer of expectant interests." Pet. App. 13a.

Although the Federal Circuit has never explained how there can be a present assignment of future unconceived, and non-existent, inventions, that common sense difficulty obviously underlay the Panel's somewhat circuitous terminology. As the Panel concluded, upon Dr. Holodniy's execution of the Cetus Agreement, "Cetus immediately gained ***equitable title*** to Holodniy's inventions" Pet. App. 14a (emphasis added), and that under *FilmTec*,

> [o]nce the invention is made and an application for patent is filed . . . legal title to the rights accruing thereunder would be in the assignee . . ., and the assignor-inventor would have nothing remaining to assign . . . . Ordinarily, no further act would be required once an invention came into being; the transfer of title would occur by

operation of law. *Id.* (quotations and citations omitted).

But the Panel also said that "while Stanford might have gained ***certain equitable rights*** against Holodniy . . . [it] did not immediately gain title to Holodniy's inventions as a result of the [Stanford agreement], nor at the time the inventions were created." Pet. App. 13a (emphasis added).

The Panel did not explain what "equitable rights" Stanford "gained." Nor did it explain how those rights differed in quantity or quality from Cetus' later acquired "equitable title," nor why or how those rights were trumped by Cetus' supposed "equitable title." Thus, the Panel did not adequately deal with another important anomaly of its reasoning–how to treat Dr. Holodniy's contract with Stanford which obviously had to have some kind of legal effect especially given the Bayh-Dole Act, and the overwhelming equities that heavily balanced in Stanford's favor.

Another anomaly of the decision below is its collateral treatment of ownership. Although the Panel concluded that pursuant to the "Visitor Confidentiality Agreement" Cetus and eventually its successor, respondent Roche, acquired a partial ownership in the three patents in suit, it also concluded that Roche was not entitled to a judicial declaration of that partial ownership because the applicable state statute of limitations period had run. Pet. App. 22a-27a.

Thus, as of this writing, it appears that the Patent Office assignment records, at least those available online, do not show Cetus or Roche as the assignee of

any ownership interest in the three patents.[6] Given the Federal Circuit's refusal to declare ownership, Roche apparently can do nothing about it.

Analytically, these are especially jarring results.

A more serious error was the Panel's failure to balance the equities between Stanford's and Roche's competing ownership claims. The Panel simply ignored or brushed aside critical facts that a court of equity would ordinarily consider, including:

- Stanford's "equitable rights" came first in time, Pet. App. 94a-95a;
- The Stanford Agreement prohibited Dr. Holodniy from entering into any agreement that created patent obligations in conflict with Stanford's rights, Pet. App. 201a;
- Only Stanford, not Cetus, received federal funding for Dr. Holodniy's research, Pet. App. 126a, 128a, 132a;
- Dr. Holodniy's work at Stanford obviously substantially contributed to the conception of these inventions and their reduction to practice, Pet. App. 34a, 95a-96a, 102a-104a;
- Stanford filed and prosecuted the patent applications practice, Pet. App. 108a;
- Cetus and then Roche never claimed ownership for 15 or more years even after they were on

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[6] *USPTO Assignments on the Web Database*, available at http://assignments.uspto.gov/assignments/?db=pat (last visited Dec. 21, 2010 – Search by Patent Number: 7,129,041, 6,503,705, and 5,968,730 in "Patent No." field.)

notice of Stanford's actions evidencing ownership practice, Pet. App. 41a, 109a-110a;

- Once the patents issued, Roche was chargeable with notice of Stanford's ownership practice, Pet. App. 125a, 127a, 131a;
- Stanford meticulously invoked its rights under the Bayh-Dole Act practice, Pet. App. 115a-116a;
- Stanford surely expended significant amounts of money, time and effort in developing and patenting these inventions; and
- Dr. Holodniy and his co-inventors executed a formal assignment to Stanford which was duly recorded at the Patent Office. (Ex. 705 to Decl. of M. Rhyu in Support of Pls.' Opp. to Defs.' Mot. for Summ. J., [D. Ct. Dkt. No. 113-8]; *see also* Pet. App. 41a, 112a.)

In light of the Panel's complete disregard of the equities, as well as its cavalier treatment of the rules of title and ownership imposed by the Bayh-Dole Act, its resort to this mechanistic and artificial dichotomy between present and future assignments is the more inexplicable.

The Panel's most substantive omission, however, was its complete failure to consider the public interest, which is often the most critical factor in a balancing of the equities. First the Panel failed to consider whether and how its ruling would affect the manufacture, marketing and distribution of this important medical innovation directed at diagnoses critical to the treatment of HIV-AIDS; how its rule would generally affect innovation in other areas of scientific and

technical endeavor; and how its ruling would "promote Science and the Useful Arts" and protect the inventor's innovation that the Patent Clause is intended to encourage and safeguard. In the context of the Bayh-Dole Act, this failure is especially important because of the Act's specifically announced purposes of promoting "the utilization of inventions arising from federally supported research or development . . . [and]] protect[ing] the public against nonuse or unreasonable use of inventions . . . ." 35 U.S.C. § 200.

C. A Critical Purpose of American Patent Law Is the Protection of the Inventor's Ownership Rights.

Article I, Section 8 of the United States Constitution gives Congress the power "To promote the Progress of Science and useful Arts, by securing for limited Times to . . . Inventors the exclusive Right to their respective . . . Discoveries . . . ."

This clause "is both a grant of power and a limitation." *Bilski v. Kappos*, 130 S. Ct. 3218, 3252 (2010) (quoting *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 5 (1966)). It "reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance in the 'Progress of Science and useful Arts.'" *Bilski*, 130 S. Ct. at 3252 (quoting *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 146 (1989)).

"This is the standard expressed in the Constitution and it may not be ignored." *Bilski*, 130 S. Ct. at 3252 (quoting *Graham*, 383 U.S. at 6 (in turn quoting *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment*

Corp., 340 U.S. 147, 154 (1950) (Douglas, J., concurring) (emphasis deleted))).

As *Bilski* notes, patent "laws which are passed to give effect to this [constitutional] purpose ought, we think, to be construed in the spirit in which they have been made." 130 S. Ct. at 3252 (quoting *Grant v. Raymond*, 31 U.S. (6 Pet.) 218, 241-42 (1832)).

Thus, it has long been the view of the Court that "the primary purpose of our patent laws is not the creation of private fortunes for the owners of patents but is 'to promote the progress of science and useful arts.' " *Motion Picture Patents Co. v. Universal Film Mfg. Co.*, 243 U.S. 502, 511 (1917). The Court emphasized this rule in *Quanta Computer, Inc. v. LG Electronics, Inc.*, 553 U.S. 617, 626 (2008), and then again last Term in *Bilski*, 130 S. Ct. at 3252.

Therefore, "[i]t is a bedrock tenet of patent law that 'an invention presumptively belongs to its creator,' " that is, the inventor. *Israel Bio-Engineering Project v. Amgen Inc.*, 475 F.3d 1256, 1263 (Fed. Cir. 2007) (quoting *Teets v. Chromalloy Gas Turbine Corp.*, 83 F.3d 403, 406 (Fed. Cir. 1996)).

This is so even if the inventor works as an employee for someone else and invents something during his term of employment.[7] *Hapgood v. Hewitt*, 119 U.S. 226

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[7] An important exception to that rule is that a person employed to invent must assign to the employer all rights to the invention and resulting patent. *Standard Parts Co. v. Peck*, 264 U.S. 52 (1924). However, it is important to note the exception to that exception arising from the

(continued...)

(1886); *Dalzell v. Dueber Watch Case Mfg. Co.*, 149 U.S. 315, 320 (1893). "[D]ue to the peculiar nature of the act of invention," the courts have been reluctant "to imply or infer an agreement by the employee to assign his patent." *United States v. Dubilier Condenser Corp.*, 289 U.S. 178, 187 (1933).[8]

Therefore, a critical focus of American Patent Law is on the protection of the inventor's rights.

These are the fundamental Constitutional principles to be applied in deciding this case.

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[7](...continued)
statutes enacted by several states providing that employee assignment agreements do not apply to inventions developed on an employee's own time with the employee's own resources. Cal. Lab. Code § 2870 (Deering 2010); Del. Code Ann. tit. 19, § 805 (2010); 765 Ill. Comp. Stat. § 1060/2 (2010); Kan. Stat. Ann. § 44-130 (2009); Minn. Stat. § 181.78 (2010); Nev. Rev. Stat. § 600.500 (2009); N.C. Gen. Stat. § 66-57-1 (2009); Utah Code Ann. § 34-39-3 (2010); Wash. Rev. Code § 49.44.140 (2010).

[8] In this situation, the employer is still entitled to a non-transferable "shop right" to practice the invention, *Dubilier Condenser*, 289 U.S. at 196, although the employee/patentee remains free to license or assign the patent to others including competitors of the employer.

D. Under Traditional Rules of Equity, as Well as Modern Contract Law, Future Inventions Cannot be Transferred in the Present and Are Subject Only to the Transfer of Equitable Title.

1. Equity long recognized that non-existent personal property could not be assigned in the present, and that contracts purporting to do so merely conveyed equitable title, enforceable by the courts of equity, requiring a subsequent act of transfer of legal title once the property came into existence.

Although at common law, mere expectancies or possibilities were not assignable, by the mid-19th Century, that rule was "much relaxed, or almost disregarded by the courts of equity." *Hinkel v. Wanzer*, 58 U.S. (17 Wall.) 353, 367 (1855).

Early commentators noted that various statutes abrogated the common law rule in particular contexts, so that contingent future interests, even possibilities, were assignable in law "*when coupled with an interest*." 3 *Pomeroy on Equity Jurisprudence* § 1287, at 3094 (4th ed. 1918) ("*Pomeroy*") (emphasis in original).

But, such statutes did not make future non-existent things immediately assignable at law because it was well accepted that "possibilities not coupled with an interest—*mere* possibilities or expectancies" were assignable only in equity. *Pomeroy*, § 1287, at 3095. It was deemed "elementary" that at law a contract for the sale of a chattel that a seller did not own did not pass legal title to the buyer without some new act by the seller after the property was acquired. *Id.*, § 1288, pp. 3098-99. But, the doctrine of equity was different. The

assignment of personal property to be acquired at a future time operated only as an equitable assignment, vesting equitable ownership in the purchaser when the property was acquired by the vendor. This ownership right was fully protected by the equity courts upon suit by the equitable assignee. *Id.*

> In truth, although a sale . . . of property to be acquired in the future does not operate as an immediate alienation at law, it operates as an equitable assignment of the *present possibility*, which changes into an assignment of the *equitable ownership* as soon as the property is acquired by the vendor. *Id.*, pp. 3103-04 (emphasis in original).

Because this ownership was equitable only, only a court of equity could turn it into "legal property, accompanied by possession." *Id.*, p. 3104.

The rule announced by Justice Story was the same. At law, an assignment of personal property was valid only if the *res* had an "actual or potential existence" at the time of the assignment. 2 *Joseph Story, Equity Jurisprudence*, § 1040, p. 407 (6th ed. 1853).

> Courts of Equity will support assignments . . . of things which have no present actual or potential existence, but rest in mere possibility; not indeed as a present positive transfer operative *in presenti*, for that can only be of a thing *in esse*, but as a present contract, to take effect and attach as soon as the thing comes *in esse*. *Id.*

Thus, until the property comes into existence, the assignee "has nothing but the contingency, which is a very different thing from the right immediately to

recover and enjoy the property." *Id.*, § 1040*b*, p. 411. "It is not an interest in property; but a mere right under the contract . . . for in the contemplation of Equity, it amounts, not to an assignment of a present interest, but only to a contract to assign when the interest becomes vested." *Id.*

2. Modern contract law has taken up the same common sense principle that a present assignment of personal property to be created or acquired in the future operates merely as a contract to assign. An assignment of "a truly future claim or interest" cannot work as a "present transfer" because "no property yet exists." Such a purported transfer is treated as "merely an agreement or promise to transfer when the capacity to transfer arises." *Stathos v. Murphy*, 26 A.D.2d 500, 503, 276 N.Y.S.2d 727, 730 (1966), *aff'd*, 19 N.Y.2d 883 (1967). *See also Ingersoll-Rand*, 110 N.J. at 624, 542 A.2d at 886 (involves post-employment inventions but discusses development and scholarly treatment of doctrine).

This principle is reflected in Section 2-105(2) of the UCC, including the version in effect in California, where the events in this case occurred:

> Goods must be both existing and identified before any interest in them can pass. Goods which are not both existing and identified are "future" goods. A purported present sale of future goods or of any interest therein operates as a contract to sell. Cal. U. Comm. Code § 2105(2) (Deering 2010) (emphasis added).

Citing that UCC section, *Williston on Contracts* teaches that "a present assignment in gross of a patent

and all future patents on improvements on the device operates as a contract to assign such future patents." 6 Richard A. Lord, *Williston on Contracts* § 13:17, at 756 (4th ed. 2006).[9]

Corbin on Contracts is to the same effect: "Courts recognize assignments of interests that do not exist [are but] mere expectancies and therefore take effect as 'equitable assignments' when the right assigned comes into existence." 9 John E. Murray, Jr., *Corbin on Contracts* § 50.2, at 229 (rev. ed. 2007).[10]

The conclusion of ancient and modern law is the same: there cannot be a present assignment of a non-existent invention; all that can be conveyed is an equitable right to an assignment when the invention comes into existence.

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[9] *Williston* also explains that "legal title to chattels subsequently to be acquired cannot be transferred without further action of the parties." 29 *Williston* § 74:15, at 327.

[10] As *Corbin* notes, *id.* at 229-30, the treatment of this problem by the *Restatement (Second) of Contracts* is wholly inadequate and inconsistent. This is so even though Comment d to Restatement Section 321 states that the effect of "a purported assignment of a future right . . . is that the assignee has enforceable rights against the assignor only to the extent that contractual remedies are available, as in the case of a promise to make a future assignment." *Restatement (Second) of Contracts*, § 321, cmt. d (1981).

E. Under this Court's Interpretations of the Predecessor of Section 261 of the Patent Act, Future Interests in Patents Can Be Assigned Only If There Is an "Inchoate Right" to That Assignment and a "Power" to Enforce It.

Those principles of equity and law are fully reflected in this Court's early patent law jurisprudence.

Section 261 of the Patent Act states that "patents shall have the attributes of personal property"[11] and that "patents, or *any interest therein, shall be assignable in law* by an instrument in writing." 35 U.S.C. § 261 (emphasis added).

Under the predecessor to that section, this Court ruled that when a party acquires "an inchoate right to [a patent], and the power to make that right perfect and absolute at his pleasure, the assignment of his whole interest, whether executed before or after the patent issued" falls within the statute. *Gayler v.*

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[11] The description of patents as "personal property" was first inserted in the Patent Law by the Patent Act of 1952, Pub. L. No. 82-593, 66 Stat. ch. 590, 792, 810 (1952). The Revision Notes of the Senate Report state that this provision "is new but is declaratory only." S. Rep. No. 82-1979 at 27 (1952), *reprinted in* 1952 U.S.C.C.A.N. 2394, 2420. Declaratory of the common law no doubt. Cf. *Taylor v. Crain*, 224 F.2d 237, 240-41 (3d Cir. 1955) (a right of common law nature further embodied in statutory terms exists as an enforceable right exclusive of the statute declaratory of it). *See also*, 1A Norman J. Singer and J.D. Shamble Singer, *Sutherland on Statutory Construction* §§ 26:1 - 26:7 (7th ed. 2009).

Wilder, 51 U.S. (17 Wall.) 477, 493 (1850) (interpreting assignment language of Section 11 of the Patent Act of 1836, Act of July 4, 1836, ch. 357, § 11, 5 Stat. 121). *See also Railroad Co. v. Trimble*, 77 U.S. (10 Wall.) 367 (1870) (assignment of patent extension); *Nicolson Pavement Co. v. Jenkins*, 81 U.S. (14 Wall.) 452 (1872) (assignment of reissued patent).

Thus, *Gayler* recognizes that an assignment of a patent must be preceded by and based upon a prior "inchoate right" and "the power to make that right perfect." *Gayler*, 51 U.S. at 493.

The conclusion to be drawn from the confluence of traditional rules of equity, modern contract law, and this Court's patent assignment jurisprudence is clear: there is no difference between Stanford's "will assign" and Cetus' "hereby assign" language. Because both simply reflect a present intention to assign non-existent unconceived inventions, they can only have created competing equitable assignments. *See Pomeroy* § 1290, at 3110 (language of present transfer or showing a present intention to make a future transfer are equivalent and merely create equitable assignments).

That should be the rule here: notwithstanding the narrow differences between the words, the Stanford and Cetus agreements should be treated as equivalent, passing only equitable title, thus requiring an additional act of transfer when the invention came into existence.

As Petitioner points out, federal courts hearing patent cases sit as courts of equity. Petitioner's Brief, p. 58 n.23. Thus the equitable title rule *amicus*

proposes will allow these courts of equity to balance the competing equitable rights that even the Federal Circuit recognized arose for both Stanford and Cetus from the fact that Dr. Holodniy executed both agreements before his inventions came into existence.

F. Important Policy Reasons, Which Are in Complete Harmony with the Bayh-Dole Act, Support the Construction of Assignments of Future Inventions to Convey Only Equitable Title.

1. Chief Justice Taney's common sense construction of assignment clauses, supported as it is by ancient rules of equity and modern contract law, is highly desirable because it allows for the consideration of competing equities based on events occurring between the execution of the assignment agreement and the creation of the invention.

In this case, there were years of intervening events which should have been considered and balanced in reaching an equitable decision: Stanford's investment of time, expense and effort; Dr. Holodniy's contract with Cetus and the work he did there; Stanford's perfection of its rights under the Bayh-Dole Act; Cetus' and then Roche's delay in acting once on notice of Stanford's assertion of ownership; Stanford's reliance on that inaction; and so on.

Such intervening equities are also painfully relevant to the protection of the rights of inventors. If "hereby assign" language operates as an immediate assignment to an inventor's employer, what happens when the employer violates the employment agreement in some material regard? What if the employer violates the law

of patenting a newly conceived invention by failing to include the identity of the true inventor in the patent applications, as Sections 111, 115 and 116 of the Patent Act expressly require? Indeed, the Patent Act requires that the true and original inventor file the patent application under oath, notwithstanding any assignment to any other person or entity. *Id.*

This latter hypothetical is not at all fanciful given the rising number of serious cases involving inventors fraudulently omitted from patent applications filed by their employers or other putative assignees.[12] It is also precisely Dr. Shukh's situation. More seriously, such misconduct constitutes *per se* inequitable conduct or fraud on the Patent Office that will invalidate a patent in derogation of an inventor's rights of inventorship.[13] A rule that would prevent an inventor from asserting claims based on such misconduct is ridiculous.

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[12] *See, e.g., Stark v. Advanced Magnetics, Inc.*, 119 F.3d 1551 (Fed. Cir. 1997); *Chou v. Univ. of Chi. & Arch Dev. Corp.*, 254 F.3d 1347 (Fed. Cir. 2001); *Shum v. Intel Corp.*, 499 F.3d 1272 (Fed. Cir. 2007); and *Larson v. Correct Craft, Inc.*, 569 F.3d 1319, 1327 (Fed. Cir. 2009).

[13] *Advanced Magnetic Closures, Inc. v. Rome Fastener Corp.*, 607 F.3d 817, 828 (Fed. Cir. 2010) (failure to disclose true inventor is inequitable conduct); *Frank's Casing Crew & Rental Tools, Inc. v. PMR Techs., Inc.*, 292 F.3d 1363 (Fed. Cir. 2002) (same); *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1321 (Fed. Cir. 2000) (same); *In re Spalding Sports Worldwide, Inc.*, 203 F.3d 800, 807 (Fed. Cir. 2000) (explaining difference between inequitable conduct and fraud on the Patent Office) (quoting *Nobelpharma AB v. Implant Innovations, Inc.*, 141 F.3d 1059, 1069-70 (Fed. Cir. 1998)).

In those situations, there are grave considerations of the public interest regarding the integrity of Patent Office proceedings that should be balanced in determining competing rights of ownership. Those rights are as serious in principle as the considerations of the public interest in this case regarding the marketing of this deeply important medical diagnostic tool.

2. Given this important context, the Federal Circuit's rule of construction completely divests inventors of important rights guaranteed them by the Patent Act, especially by Section 256 for the correction of inventorship. Based in large part on its artificial dichotomy, the Federal Circuit is developing a body of law to the effect that an inventor who has assigned his inventions to an employer does not have Article III standing to sue for the correction of inventorship under Section 256 because the inventor no longer has a stake in the inventions. *See, e.g., Larson*, 569 F.3d 1319; *Jim Arnold Corp. v. Hydrotech Systems, Inc.*, 109 F.3d 1567, 1571-72 (Fed. Cir. 1997).

Thus, under this supposed rule of standing, if "hereby assign" language of an employment agreement operates as an immediate assignment of future inventions, then an inventor whose rights have been violated by the employer may lack standing to sue notwithstanding the employer's intervening misconduct, inequitable acts, and failure to live up to its obligations under the agreement. Indeed, in that situation, an inventor who is fraudulently omitted by the employer from a patent application in violation of Sections 111, 115, and 116 does not have standing to seek redress for that illegal conduct by suing to correct inventorship under Section

256 of the Patent Act. 35 U.S.C. § 256. Such a rule is nonsensical and substantially contrary to the policy behind the Patent Clause of the protection of inventors.

3. On the other hand, the rule of equitable assignments advocated by Dr. Shukh will not interfere with the rights of employers to their employees' inventions. Once an invention comes into existence, employers merely need to obtain a formal assignment from the employee as originally agreed.

This is nothing new. In fact, Rule 3.73 of the Patent Office's Manual of Patent Examining Procedure (MPEP), 37 C.F.R. § 3.73, requires any patent applicant to establish the right to prosecute the patent application by submitting sufficient documentary proof of ownership including "[d]ocumentary evidence of a chain of title from the original owner to the assignee (e.g., copy of an executed assignment)." 37 C.F.R. § 3.73(b)(1)(i).[14] This is the usual custom and practice for employee inventions and patenting as shown by the language of the Stanford Agreement and Dr. Holodniy's execution of the actual assignment that conveyed title and ownership and was recorded at the Patent Office.

Therefore, all contract provisions requiring the assignment of future inventions – whether they say "hereby assign" or "will assign"– should be treated as

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[14] "Although, the MPEP 'does not have the force of law or the force of the rules of Title 37 of the Code of Federal Regulations,' MPEP Foreword (8thed., Jul. 2010 rev.), it 'is made available to the public and . . . describe[s] procedures on which the public can rely.' " *In re Skvorecz*, 580 F.3d 1262, 1268 (Fed. Cir. 2009).

equivalent. This will merely require an employer to obtain a formal assignment when the invention is conceived and reduced to practice, something the employer must already do under Patent Office practice and procedure. If any intervening equities arise that might nullify such an assignment, the inventor still has a remedy to invoke those equities and protect his or her inventorship rights. This rule of fundamental fairness imposes no hardship on either an employer or an inventor, and still preserves the rules of equity and of contract law.

4. The equitable title rule advocated by Dr. Shukh would be fully consistent with a construction of the Bayh-Dole Act that protects the rights of institutional assignees when, during the course of federally funded research, its employees conceive and reduce to practice inventions that are then patented. This is especially important because the Bayh-Dole Act must be harmonized with Section 261 that allows the assignment of patents and any interest therein. 35 U.S.C. § 261.

The relationship between an employer and an inventor working on such a federally funded project is akin to that of an inventor who is "employed to invent" but who is under no contractual obligation to assign his inventions or patents. In the latter situation it is well accepted that the employer has an enforceable equitable right to require an employee to assign any inventions and patents. *Standard Parts*, 264 U.S. at 58; *see also*, Argument, *supra*, n.7, p. 16 and accompanying text.

For one thing, unlike this case, it must often be the case that inventors sign assignment agreements with

no advance intention of working in federally funded programs that might result in Bayh-Dole Act patents.[15] Therefore, ownership rights between an inventor and his employer and any third party to any future inventions must be subject to the usual default rules described above. *See* Argument, *supra*, p. 16 & n. 7.

Thus, the Bayh-Dole Act rules cannot kick in until an invention is created from federally funded contracts or research. Only at that point does the Act alter the usual rules of title by establishing a conditional hierarchy of ownership rights.[16] Once the Act's rules of ownership priority do attach, all the three affected participants – the institution, the Government, and the inventor – have conditional "inchoate" rights. The institution has the right to "retain title," but only if it follows a strict set of procedures designed to effectuate the public purposes of the Act – notice, prompt prosecution of the patent and so on. 35 U.S.C. § 202(a) & (c).[17]

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[15] In this case, when Dr. Holodniy joined Dr. Merrigan's lab, the work he got involved in was funded by NIH. JA 95, 98.

[16] Although, as the Panel below noted, the primary purpose of the Bayh-Dole Act is to regulate relationships of federal funds grantees with the Government, not the relationship between the inventor and the grantees, 583 F.3d at 845 (citing *Fenn v. Yale Univ.*, 393 F. Supp. 2d 133, 141 (D. Conn. 2004), *aff'd on other grounds*, 184 Fed. Appx. 21 (2d Cir. 2006), there can be no question that the Act controls the sequence of ownership rights of the institution, the Government and the inventor.

[17] Subsection 202(a) expressly makes the institution's (continued..)

Similarly, the Government's right to title is conditional at least in part on the failure of the institution or contractor to perfect its rights. If the institution or contractor fails to follow the prescribed steps to perfect title, the Government can then step in and take title. *Campbell Plastics Eng'g & Mfg. v. Brownlee*, 389 F.3d 1243, 1247 (Fed. Cir. 2004). Likewise, the inventor's rights are conditioned on the institution's election not to retain title and the Government's consideration of "requests for retention of rights by the inventor." 35 U.S.C. § 202(d).

These are all "inchoate rights" and all three participants have, to varying degrees, "the power to make th[ose] right[s] perfect" by taking various steps and doing various things.[18]

Thus, for example, by the terms of the Bayh-Dole Act, even if Dr. Holodniy had *not* executed an assignment agreement, Stanford would have been vested with equitable "inchoate right" to his future inventions resulting from federal funding. Once the inventions came into existence, Stanford had "the power to make that right perfect" by following the Bayh-Dole Act procedures and then requiring him to provide a formal assignment.

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[17](...continued)
election to retain title "subject to" the steps outlined in subsection 202(c).

[18] This view is also confirmed by the implementing regulations, 37 C.F.R. § 401.1, *et seq.*, esp. § 401.14 (specifying procedures for the implementation of the Act's conditional rights and procedures to perfect them). See Petitioner's Brief, pp. 15-16.

And, that's precisely what happened: the University perfected its Bayh-Dole Act rights to retain title by giving the required notice, applying timely for the patents, and so on. *See* Petitioner's Brief, p. 21. To close the loop of title, it also obtained an instrument of assignment from Dr. Holodniy that was recorded at the Patent Office. (Ex. 705 to Decl. of M. Rhyu in Support of Pls.' Opp. to Defs.' Mot. for Summ. J., [D. Ct. Dkt. No. 113-8]; *see also* Pet. App. 41a, 112a.)

As the Federal Circuit correctly noted in *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 929 (Fed. Cir. 2004), the Bayh-Dole Act did not relax the statutory requirements for patentability under Section 112 of the Patent Act. 35 U.S.C. § 112. Nor should it alter the statutory requirements of Section 261, the traditional rules of equity, the modern doctrines of contract law, or this Court's jurisprudence regarding the assignment of interests in future inventions and future patent rights.

Moreover, even with these clear rules under the Bayh-Dole Act, Cetus must have had some kind of rights arising from its contract with Dr. Holodniy. For example, what if Stanford and the Government had decided not to take title, the Government allowed him to retain title, but then he decided he wanted to keep the invention despite his agreement with Cetus? Cetus clearly would have some kind of colorable rights under its agreement.

What if the dispute between Stanford and Cetus concerned whether the invention in fact resulted from federally funded research? If it were found that no federal funding was involved in the invention, what rules would pertain to decide the dispute about

ownership between Stanford and Cetus? This situation has already arisen and seems likely to reoccur. *Ciba-Geigy Corp. v. Alza Corp.*, 804 F. Supp. 614, 627 (D.N.J. 1992).

Thus, it is clearly inadvisable to give the Bayh-Dole Act a guillotine effect of cutting off the rights of everyone except the institution receiving the federal funding. Because of these overlapping rights, it is also not advisable to decide this case under the Bayh-Dole Act based on an assignment regime different than that applicable to purely private, non-Bayh-Dole Act situations. After all, Section 261 says that patents and all interests in them are assignable, so that must include patents covered by the Bayh-Dole Act after its procedures are exhausted.

If this Court leaves the Federal Circuit's artificial dichotomy intact, by ruling that it is irrelevant to ownership of Bayh-Dole Act patents, it is sure that the two conflicting assignment doctrines will eventually collide and introduce even more uncertainty into an area of great importance – the intersection between science and technology, on the one hand, and business and the law, on the other.

CONCLUSION

The judgment of the court of appeals should be reversed and the case remanded for further proceedings.

Respectfully submitted,

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APPENDIX

APPENDIX OF CONSTITUTIONAL, STATUTORY AND REGULATORY PROVISIONS

The Constitutional Provision, Section of the Patent Act, and Patent Office Regulation believed by *amicus* to be involved herein are as follows:

United States Constitution, Article I, Section 8.

> The Congress shall have the Power . . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.

35 U.S.C. § 261 Ownership; assignment.

> Subject to the provisions of this title, patents shall have the attributes of personal property.
>
> Applications for patent, patents, or any interest therein, shall be assignable in law by an instrument in writing. The applicant, patentee, or his assigns or legal representatives may in like manner grant and convey an exclusive right under his application for patent, or patents, to the whole or any specified part of the United States.
>
> * * *
>
> An assignment, grant, or conveyance shall be void as against any subsequent purchaser or mortgagee for a valuable consideration, without notice, unless it is recorded in the Patent and Trademark Office within three months from its date or prior to the date of such subsequent purchase or mortgage.

37 C.F.R. § 3.73 Establishing right of assignee to take action.

(a) The inventor is presumed to be the owner of a patent application, and any patent that may issue therefrom, unless there is an assignment. The original applicant is presumed to be the owner of a trademark application or registration, unless there is an assignment.

(b)(1) In order to request or take action in a patent or trademark matter, the assignee must establish its ownership of the patent or trademark property of paragraph (a) of this section to the satisfaction of the Director. The establishment of ownership by the assignee may be combined with the paper that requests or takes the action. Ownership is established by submitting to the Office a signed statement identifying the assignee, accompanied by either:

(i) Documentary evidence of a chain of title from the original owner to the assignee (e.g., copy of an executed assignment). . . . For patent matters only, the submission of the documentary evidence must be accompanied by a statement affirming that the documentary evidence of the chain of title from the original owner to the assignee was or concurrently is being submitted for recordation pursuant to § 3.11; or

(ii) A statement specifying where documentary evidence of a chain of title from the original owner to the assignee is recorded in the assignment records of the Office (e.g., reel and frame number).

(2) The submission establishing ownership must show that the person signing the submission is a person authorized to act on behalf of the assignee by:

(i) Including a statement that the person signing the submission is authorized to act on behalf of the assignee; or

(ii) Being signed by a person having apparent authority to sign on behalf of the assignee, e.g., an officer of the assignee.

(c) For patent matters only:

(1) Establishment of ownership by the assignee must be submitted prior to, or at the same time as, the paper requesting or taking action is submitted.

(2) If the submission under this section is by an assignee of less than the entire right, title and interest, such assignee must indicate the extent (by percentage) of its ownership interest, or the Office may refuse to accept the submission as an establishment of ownership.

AMICUS CURIAE BRIEF

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IN THE

Supreme Court of the United States

BOARD OF TRUSTEES OF
LELAND STANFORD JUNIOR UNIVERSITY,
Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC. *et al.*,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICUS CURIAE* JOHN SUTTON SUGGESTING REVERSAL

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QUESTION PRESENTED

"Whether a federal contractor university's statutory right under the Bayh-Dole Act, 35 U.S.C. §§ 200-212, in inventions arising from federally funded research can be terminated unilaterally by an individual inventor through a separate agreement purporting to assign the inventor's rights to a third party."

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IN THE

Supreme Court of the United States

No. 09-1159

BOARD OF TRUSTEES OF
LELAND STANFORD JUNIOR UNIVERSITY,
Petitioner,

v.

ROCHE MOLECULAR SYSTEMS, INC. *et al.*,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICUS CURIAE* JOHN SUTTON SUGGESTING REVERSAL

INTEREST OF *AMICUS CURIAE* [1]

John P. Sutton is a registered patent lawyer with half a century in the field. He is writing a book analyzing every decision of the two patent courts (the Court of Customs and Patent Appeals and the Court of Appeals for the Federal Circuit) that has been reviewed by this Court.

[1] Under Rule 37.6, this brief is not authored in whole or in part by counsel for any party. No person has made a monetary contribution to the preparation or submission of this Brief. Petitioner and Respondents have consented to the filing of all briefs *amicus curiae*.

He has no connection, professionally or privately, with any party to this litigation.

SUMMARY OF ARGUMENT

The Federal Circuit erred in "vacat[ing] the district court's judgment of invalidity" in order to address the ownership issue. "[V]alidity has the greater public importance" *Cardinal Chemical Co. v. Morton Int'l, Inc.*, 508 U.S. 83, 100 (1993). "We have also emphasized the importance to the public at large of resolving questions of patent validity in *Blonder-Tongue Laboratories v. University of Ill. Foundation*, 402 U.S. 313" (1971) (*id.*).

If no property right exists, it matters not who has the superior right to the property. The Government, the university, the Roche entities, and the inventors cannot "own" it.

The Federal Circuit erred as a matter of law in elevating a visitor's agreement to a level that overrides an Act of Congress, the common law, and this Court's precedents.

ARGUMENT

The Federal Circuit is a specialized patent court. It succeeded the first patent court, the Court of Customs and Patent Appeals (CCPA), which originally was a legislative court charged with reviewing appeals from the Patent and Trademark Office, a federal administrative agency. The CCPA did not defer to findings of fact by the agency experts. It routinely substituted its view of facts for that of the Patent Office.

Because the CCPA judges became Federal Circuit judges in 1982, the reluctance to defer to the facts

found by the trier of facts continued after 1982. The lack of deference to decisions of the Patent Office extended to decisions of United States District Courts, at least initially.

In 1986, this Court vacated a Federal Circuit decision that substituted the Federal Circuit's view of the facts for the view of the district court without finding clear error (*Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809 (1986)).

The district court had held that Panduit's patents were invalid. The Federal Circuit reversed the decision of the district court because it disagreed with the findings. The 22-page decision of the Federal Circuit (*Panduit Corp. v. Dennison Mfg. Co.*, 774 F. 2d 1082) never mentions the requirement of Fed. R. Civ. P, 52(a)(6) that findings may not be set aside unless clearly erroneous. This Court granted the petition, the Federal Circuit decision was vacated and remanded summarily, all in a *per curiam* order.

The present case resembles *Dennison* in that the Federal Circuit vacated the district court holding of invalidity in each one. Based upon the evidence submitted by Respondents, the district court granted the Respondents' motion and held the patents invalid. The Federal Circuit found no clear error in the district court decision. Indeed, the Federal Circuit apparently agreed with the decision. In the absence of a showing of clear error, the decision should not have been vacated.

The validity determination is dispositive of this case. There can be no ownership issue if there is no patentable invention. Bayh-Dole defines "invention" as "any invention or discovery which is or may be patentable" (35 U.S.C. § 201(d)). None of the Federal

agency, the contractor, the inventor, or the accused infringer has any property right in the invalid patents.

The Federal Circuit also vacated a judgment of patent invalidity of a district court in *Cardinal Chemical, supra*. The Federal Circuit there found no clear error in the district court decision, and made no reference to the Rule 52(a)(6) requirement of deference to district court findings, just as in *Dennison* and as in this case.

This Court pointed out that "the Federal Circuit is not a court of last resort. If that court had jurisdiction while the case was pending before it, the case remains alive (barring other changes) when it comes to us. . . . [W]e are not prevented from considering the question of validity merely because a lower court thought it superfluous" (508 U.S. at 97).

At 100, this Court said, "our prior cases have identified a strong public interest in the finality of judgments in patent litigation. In *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327[, 330] (1945) . . . we stated that 'of the two questions [validity and infringement], validity has the greater importance, [and the better practice is] inquiring fully into the validity of this patent.' We also emphasized the importance to the public at large of resolving questions of patent validity in *Blonder-Tongue*," *supra*.

The decision to vacate the holding of invalidity here is erroneous and must be vacated under Rule 52(a)(6) and this Court's precedents.

The question presented here relates to the ownership issue. The Federal Circuit, in result-oriented decision-making, set aside the invalidity decision of

the district court in order to find that Respondents owned the patents. Again, there was no Rule 52(a)(6) identification of clear error by the district court. The Federal Circuit simply disagreed with the weight given to certain facts by the district court and substituted its own view of the weight to be accorded facts.

The district court here found it important that Petitioner, as a "contractor" for funding by NIH, granted a license to the government pursuant to the Bayh-Dole Act to use the patented inventions. It was ignored by the Federal Circuit, which instead substituted its view that a single one of many contracts superseded other contracts and the Act of Congress sorting rights to patents.

Respondents contended that the assignment contracts signed by all inventors to Petitioner were superseded by a contract signed by the junior-most member of the Petitioner's research team. The Federal Circuit reasoned that the "Visitor's Confidentiality Agreement (VCA)" that Dr. Holodniy was required to sign to enter Cetus premises gave Respondents superior rights to ownership of the patents assigned to Petitioner.

That reasoning is wrong. A contract between a visitor and a company visited is not an employment contract. Cetus did not *hire* Dr. Holodniy. He was hired by Petitioner as a Research Fellow and was paid a salary (presumably with NIH funds) by Petitioner.

The co-inventors of the patents-in-suit were hired by Petitioner as well, and assigned their rights to Petitioner. The funds granted to Petitioner under the NIH contract complicates the master-servant rela-

tionship, but is within the purview of the Bayh-Dole Act.

At common law, a person hired to invent must assign his rights to patents made during employment and using facilities and resources of the employer. This Court used the term "paymaster" for the employer of such a person hired to invent. In *United States v. Dubilier Condenser Corp.*, 289 U.S. 178, 187 (1933) the common law view was expressed this way:

> "One employed to make an invention, who succeeds, during his term of service, in accomplishing that task, is bound to assign to his employer any patent obtained. The reason is that he has only produced that which he was employed to invent. His invention is the precise subject of the contract of employment. A term of the agreement necessarily is that what he is paid to produce belongs to his paymaster. *Standard Parts Co. v. Peck*, 264 U.S. 52 (1924). On the other hand, if the employment contract be general, albeit it covers a field of labor and effort in the performance of which the employee conceived the invention for which he obtained a patent, the contract is not so broadly construed as to require an assignment of the patent."

Respondents claim entitlement to shop rights under the common law. Does the Visitor's contract meet the common law contract of hired to invent? The answer is emphatically "NO."

Dr. Holodniy was hired by Petitioner, not Respondents. He and his superiors on the research team were paid by Petitioner, their "paymaster." His superiors were undoubtedly aware that Dr. Kary Mullis had published in 1985 a paper regarding PCR.

Polymerase Chain Reaction (PCR) is the use of *Thermus Aquaticus* DNA polymerase for amplifying DNA. "Typically, it takes just a few hours to amplify a DNA sequence a millionfold." Mullis received the 1993 Nobel Prize for PCR, an invention assigned to Cetus. (Sadava, Course Guidebook, "*Understanding Genetics*," (The Teaching Company, 2008) p. 77).

("Chain Reaction" is a bit of a misnomer for replicating RNA. The term historically means instantaneous explosion of energy by fusion or fission. Further, amplification is creative, not destructive.)

It was knowledge of the Cetus work by Petitioner's research team that led the district court to hold that it was "obvious to try" PCR for amplifying DNA in HIV virus, citing *KSR International Co. v. Teleflex, Inc.*, 553 U.S. 398 (2007).

Petitioner did not ask Cetus to resolve a problem with the HIV assay. Rather, Petitioner's research team knew what DNA it wanted replicated. What the team lacked was knowledge of how to use PCR. The bargain was that Cetus would be paid for transferring know-how and materials to Petitioner's team. The new Research fellow was the vehicle for the transfer.

This cannot fairly be described as hiring Holodniy to invent, justifying an assignment of the Petitioner's assay to Respondents. Surely, Cetus did not prove that the "invention [by Petitioner's research team] is the precise subject of the contract of employment" of Holodniy, within the meaning of *Dubilier*.

Holodniy was never employed by Cetus, paid by Cetus, or contributed anything to Cetus. It cannot be said that Holodniy "has only produced that which he was employed to invent."

Dubilier is instructive in resolving this dispute for other reasons. Justice Stone dissented, joined by Justice Cardozo and Chief Justice Hughes. Several insightful passages help to resolve this dispute.

1. FACT QUESTION

At 289 U.S. 214, Justice Stone wrote, "What the employee agrees to assign to his employer is always a question of fact. It cannot be said that merely because an employee agrees to invent, he always agrees to assign any patent secured for the invention. Accordingly, if an assignment is ordered in such a case it is no more to be explained and supported as the specific enforcement of an agreement to transfer property in the patent than is the shop-right which equity likewise decrees, where the employment does not contemplate invention. All the varying and conflicting language of the books cannot obscure the reality that in any case where the rights of the employer are not fixed by express contract, and no agreement in fact may fairly be implied, equity determines after the event what they shall be. In thus adjudicating *in vivitum* the consequences of the employment relationship, equity must reconcile the conflicting claims of the employee who has evolved the idea and the employer who has paid him for his time and supplied the materials utilized in experimentation and construction."

It is thus a matter of equity to reconcile the positions of the parties. Cetus was not an employer; did not pay Holodniy for his time, and did not supply the materials utilized in experimentation and construction.

If what is to be assigned is a question of fact, as the *Dubilier* dissent says, the visitor's contract cannot be

a present assignment of the inventions later patented and assigned to Petitioner. The contract does not define any invention that Holodniy was assigned to invent. The language "I will assign and hereby do assign" does not relate to any specific invention, as a matter of fact. "[I]deas, inventions and improvements" in the visitor's form agreement certainly does not specify what Holodniy was assigned to invent. ("Ideas" in the visitor's agreement may be summarily dismissed as not patentable subject matter, unlike patentable "inventions" and 'improvements" under 35 U.S.C. § 101.)

Holodniy had no interest in any invention when he signed the visitor's paper indicating both a future and a present assignment to Cetus. There was absolutely nothing in Holodniy's mind about the wisdom of using PCR to amplify DNA when he signed what the Federal Circuit characterized as a "present assignment."

If, as Roche now contends, the invention was the result of consulting with Cetus, then the VCR could not possibly be a present assignment because it was signed before he visited Cetus. If the invention was derived from Cetus, it could not have been assigned before his collaboration with Cetus

Moreover, because Holodniy was the junior-most of three inventors in the patents prosecuted by Stanford, Cetus cannot claim ownership of all three of the patents. The other inventors did not sign the visitor's contract that Holodniy signed. They agreed to receive material transfers, but not to assign future inventions to Cetus. The other co-inventors, like Holodniy, had already assigned future inventions to Petitioner.

Further, Cetus cannot claim rights to the work the Stanford team did under an NIH contract. NIH provided no funds to Cetus, and Cetus had no obligation to give the Government any rights. The first contract was between the Government and Petitioner under the Bayh-Dole Act. No later contract can supersede that original contract.

If a court of equity is to weigh the equitable interests in this case, then Respondents have a weak position.

In addition, Respondents position is weak under Federal Rule 56. The Federal Circuit conceded that on summary judgment, all evidence is to be viewed "in the light most favorable to the non-moving party."

The evidence shows that Holodniy assigned future inventions to petitioner on June 28, 1988. He assigned future inventions to Cetus on February 14, 1989, eight months later. Viewing the evidence in the light most favorable to Petitioner, it has the prior right. The visitor agreement requires that the visitor "will assign" future inventions to Cetus. The addition "I do hereby assign" ideas, inventions and/or improvements must mean any that are now in existence, reading the document in a light favorable to Petitioner. That is, "will assign" in the visitor's agreement relates to future ideas not yet existing, and "do assign" relates to ideas already in existence.

Further guidance to the application of Rule 56 is provided in the Advisory Committee Notes. The Note accompanying the 1963 Amendment reads, "The very mission of the summary judgment procedure is to pierce the pleadings and to assess the proof in order to see whether there is a genuine issue for trial."

Instead of substituting its view of the visitor's agreement as a present assignment of ideas, inventions, and improvements not yet in existence (thereby superseding the prior assignment to Petitioner), the Federal Circuit should have remanded the case for trial of the issue in the district court.

The 1963 Note also states, "Where an issue as to a material fact cannot be resolved without observation of the demeanor of witnesses in order to evaluate their credibility, summary judgment is inappropriate. Where the evidentiary matter in support of the motion does not establish the absence of a genuine issue, summary judgment must be denied even if no opposing evidentiary matter is presented."

The court of appeals cannot decide that the visitor's agreement is a present assignment of an invention that has not yet been conceived in a motion for summary judgment. If Justice Stone was correct in "[w]hat the employee agrees to assign to his employer is always a question of fact," summary judgment is inappropriate. "Present assignment" is a disputed material fact.

II. SHOP RIGHT IF NOT HIRED TO INVENT

Justice Stone's dissent continues at 215. "Where the employment does not contemplate the exercise of inventive talent the policy of the patent laws to stimulate invention by awarding the benefits of the monopoly to the inventor and not to someone else leads to a ready compromise: a shop-right gives the employer an adequate share in the unanticipated boon." There is no employment contract between Holodniy and Cetus. Cetus did not "contemplate the exercise of inventive talent" by the visitor. The visitor was not paid and Cetus did not receive "unanticipated boon."

III. PUBLIC FUNDS; PUBLIC ENTERPRISE

The dissent by Justice Stone noted at 217 that the inventors were "part of a public enterprise. It was devoted to the improvement of the art of radio communication for the benefit of people of the United States, carried on in a government laboratory, maintained by public funds, . . . For the work to be successful, the government must be free to use the results for the benefit of the public in the most effective way." These arguments support the operation of the Bayh-Dole Act. They do not support Respondents.

IV. PRESERVATION OF HUMAN LIFE

Finally, the Stone dissent at 218 specifies public purposes. "The case would be more dramatic if the inventions produced at the public expense were important to the preservation of human life, or the public health." This case involves measuring the virus in blood samples of AIDS patients to determine the effectiveness of drug treatments. What could be more "important to the preservation of human life, or the public health"?

Thus, both the majority and the dissenting opinions in *Dubilier* require that the Respondents' ownership arguments must be rejected.

CONCLUSION

Rule 52 bars vacating the district court's determination of invalidity of the patents in the absence of clear error. The Federal Circuit decision vacating the invalidity ruling must be vacated. Resolving the issue of validity of patents is in the public interest. The invalidity issue is dispositive in this case. An

invalid patent is in the public domain, free for all to use.

The Federal Circuit erred in holding that the visitor's agreement trumps the Bayh-Dole Act and the prior contracts with Petitioner. Petitioner's position on the ownership issue is correct, but no party can own an invalid group of patents.

There is a genuine issue of material fact whether the visitor's contract is an employment contract and whether the contract is a present assignment of something not yet existing. The Federal Rule 56 and this Court's precedents require vacating the decision of the court of appeals.

Respectfully submitted,

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